Chapter 4	Chapter 5	Chapter 6	Chapter 7
Fungi	**Protozoa and metazoa**	**Spirochaetes**	**Myco-bacteria**
Superficial Dermatophytes Nocardia minutissimus Candida albicans Malassezia furfur *Systemic* Actinomyces israeli[1] Aspergillus fumigatus Cryptococcus neoformans Histoplasma capsulatum Blastomyces dermatitidis Coccidioides immitis Sporotrichum schenkii	*Protozoa* Entamoeba histolytica Trypanosoma Leishmania Plasmodia Toxoplasma Trichomonas Giardia lamblia Balantidium coli *Metazoa* Trematodes (flukes) Cestodes (tapeworms) Nematodes (round worms)	*Treponema* Trep pallidum Trep pertenue Trep carateum *Borrelia* Bor recurrentis Bor vincenti *Leptospira* L icterohaemorrhagiae L. canicola	Myco tuberculosis Myco leprae
		Penicillin Tetracyclines Chloramphenicol Bacitracin	Streptomycin Isoniazid P.A S Neomycin

[1] Actinomyces israeli often sensitive to penicillin streptomycin tetracyclines and erythromycin

pter 7	Chapter 8	Chapter 9	Chapter 10	Chapter 11	
pro- teria	Gram positive bacteria	Gram negative bacteria	Rickettsiae	Viruses	
				Large	Small
ulosa prae	Diplococcus pneumoniae Streptococcus pyogenes Staphylococcus aureus Corynebacterium diphtheriae Clostridia Bacillus anthracis Erysipelothrix rhusiopathiae	*Neisseria*[a] N meningitidis N gonorrhoeae *Haemophilus* H pertussis H ducreyi H influenzae *Brucella* Br abortus Br melitensis Br suis *Enteric Group* Escherichia coli Aerobacter aerogenes Klebsiella pneumoniae Proteus Pseudomonas Salmonella Shigella *Pasteurella* Past pestis Past tularensis *Vibrio cholerae*	R. prowazeki R. mooseri R. tsutsugamushi R. rickettsi R. conori R. pijperi R. akari R. burneti R. quintana	Psittacosis Lymphogranuloma venereum Trachoma Inclusion conjunctivitis Cold haemagglutinin	Mumps Variola Rabies Varicella Herpes zoster Herpes simplex Influenza Lymphocytic choriomeningitis Sandfly fever Arthropod borne encephalitis Dengue Yellow fever Poliomyelitis Coxsackie Measles Rubella Common cold Adenovirus H patitis Infectious mononucleosis
mycin and cin	Sulphonamides Penicillin Tetracyclines Chloramphenicol Erythromycin Oleandomycin Carbomycin Spiramycin Bacitracin Vancomycin Novobiocin	Sulphonamides Streptomycin Tetracyclines Chloramphenicol Polymyxin Neomycin	Tetracyclines Chloramphenicol	Tetracyclines Chloramphenicol	

cyclines and

[a] Neisseria are also susceptible to agents effective against Gram positive bacteria

THE DIAGNOSIS AND TREATMENT OF INFECTIONS

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PREFACE

THE medical graduate has gained his knowledge of the diagnosis and treatment of infections from the bacteriology department from his visits to fever hospitals and from various clinical specialties These varied backgrounds provide a stimulating crossfire of divergent views but they confuse the student when the opinions are discordant With rapid advances in specific chemotherapy and more precise methods of diagnosis close liaison between the clinician and laboratory worker becomes obligatory For this reason the student should be taught to think in terms of both clinical and laboratory aspects of an infection rather than retain them in two watertight compartments The aim of this book is to synthesise these two disciplines for the student and practitioner and for the mutual benefit of clinician and laboratory worker It is hoped that the common ground may help the one to appreciate the difficulties of the other

The book has been arranged in three parts Part 1 provides a pen picture of the currently used chemotherapeutic agents emphasising their antimicrobial range indications for their use fate in the body and complications following their use It is as up to date as possible in this rapidly changing field of therapeutics Part 2 describes the micro-organisms responsible for human infections Diagnostic methods which should be known to the clinician are included but not those technical details which are dealt with in textbooks of bacteriology Finally Part 3 describes infections as they present in various systems This final section provides the setting for synthesising knowledge of the causal agent and its specific chemotherapy as outlined in Parts 1 and 2

There is some inevitable overlap but repetition has been reduced to a minimum Some of the micro organisms have not fitted conveniently into any particular system of Part 3 so the clinical infection they produce and the treatment have been included in Part 2 Charts have been added because medical students have shown their eagerness to have their thoughts collected for them just before their final examinations Busy house officers and registrars might also find some use for these charts as a ready reckoner

The nomenclature used with few exceptions is that of Bergey s *Manual of Determinative Bacteriology* 6th Edition 1948 London Baillière Tindall and Cox Ltd The exceptions due to their

familiarity and wide acceptance in this country, have been *Staphylo coccus aureus* for *Micrococcus pyogenes, var aureus* and *Pseudomonas pyocyanea* for *Pseudomonas aeruginosa* There are occasional lapses into the more flexible and colloquial terms such as streptococcus, gonococcus and meningococcus for some of the pyogenic cocci

If references were included to provide fair coverage of all aspects of this book its size would inevitably be swollen Selected additional reading for each chapter would demand delicate judgment and even so lead to grave omissions References have therefore been restricted to the original descriptions of each of the chemo therapeutic agents These supply the historical background for Table 2 from which the reader can gain some sort of perspective of their rate of introduction during the last quarter of a century

Dr Yale Kneeland Jr, stimulated my interest in infections and taught me to bridge the gap between the ward and laboratory Mrs Katherine Mills Price endeavoured to inculcate in me her efficient laboratory discipline I am greatly indebted to them and to their colleagues for facilities and memorable hospitality at the Presbyterian Medical Center and College of Physicians and Surgeons, New York City Dr Francis O Grady Bland Sutton Institute of Pathology Middlesex Hospital Medical School not only read the whole manuscript but gave invaluable suggestions at all stages of its preparation Dr W R Thrower and Mr G Bryan kindly checked portions of it Thereafter the co-operation of Mr Per Saugman and the staff of Blackwell Scientific Publications Ltd guided the book with the minimum of personal inconvenience to its present form

So far this brief outline of the evolution of the book has made no mention of its source of inspiration For there is one person whose personal example sparked it off and whose unflagging energy prevented it from being discarded in its unbound state Those who are sufficiently enquiring to read thus far in a preface will have no difficulty in recognising this particular mentor They will realise that her participation from start to finish entitles my wife Dr Sheila Sherlock to co-authorship

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TABLES

PART 1

CHEMOTHERAPEUTIC AGENTS

CHAPTER 1

CHEMOTHERAPEUTIC AGENTS

Drugs used in the treatment of infections include true antibiotics isolated from micro-organisms and also various synthetic substances to which the term antibiotics cannot be strictly conferred The term chemotherapeutic agent is used to cover substances of any source which are of value in the treatment of infections in man and in animals This chapter outlines their historical introduction antimicrobial range of activity broad indications for their use the forms in which they are employed and the recommended doses of each product The fate in the body of each drug and its toxicity is discussed in succeeding chapters

SULPHONAMIDES

A report of the red dye prontosil by Domagk in 1935 (Table 2) was soon followed by the demonstration that its activity depended upon sulphanilamide and analogues of this with a wider anti bacterial range soon became available The sulphonamides were revolutionary in that small concentrations inhibited the growth of bacteria without injuring the tissues of the host

Antimicrobial range

The bacteriostatic range of the sulphonamides includes both Gram positive and Gram negative organisms

Indications

The introduction of non toxic antibiotics has inevitably lessened the indications for sulphonamides which are now mainly reserved for the following conditions

1 Meningococcal meningitis The absorbable sulphonamides traverse the blood brain barrier in high concentration and so they are preferable to intramuscular penicillin
2 Bacillary dysentery for which both the absorbable and unabsorb able sulphonamides are often effective
3 As an alternative to penicillin for streptococcal pneumococcal and gonococcal infections especially when the patient is allergic to penicillin

4 Acute urinary tract infections due to Escherichia coli
5 In combined chemotherapy particularly with streptomycin in brucellosis or with penicillin or tetracycline in actinomycosis
6 Soft sore due to H ducreyi because concomitant syphilitic infection is not masked as might occur when penicillin is used
7 Mass prophylaxis in a closed community when meningococcal meningitis or streptococcal sore throats are prevalent

Forms

The British Pharmaceutical Codex (1954) lists nine absorbable sulphonamides and three which are only poorly absorbed from the intestine The absorbable sulphonamides are sulphacetamide sulphadiazine sulphadimidine sulphafurazole sulphanilamide sulphamerazine sulphapyridine sulphasomidine and sulphathiazole The poorly absorbed or gut active compounds are phthalylsulpha thiazole succinylsulphathiazole and sulphaguanidine There are sodium derivatives of sulphadiazine sulphadimidine sulpha merazine sulphapyridine and sulphathiazole as well as sulpha furazole diethanolaminate for parenteral use whilst sodium sulpha cetamide and sulphafurazole are often recommended for topical application

The disadvantage of the highly alkaline sodium sulphonamides may be avoided by using a derivative of sulphathiazole thiasolucin, which is in neutral solution for either intravenous or intramuscular routes when parenteral administration is indicated

Each type of sulphonamide is uniformly issued as a 0 5 g tablet A sulphatriad tablet is compounded of sulphathiazole (0 185 g) sulphadiazine (0 185 g) and sulphamerazine (0 13 g) and each teaspoonful of a syrup suspension is roughly equivalent to a 0 5 g tablet There is also a syrup containing N acetyl sulphafurazole

In the American literature sulphafurazole is called sulfisoxazole sulphadimidine is officially known as sulfamethazine or sometimes called sulfamezathine and sulphasomidine is known as sulfadimetine

Dosage

Dosage (4 to 8 g daily) varies from one sulphonamide to another depending on its speed of absorption acetylation and excretion It also depends on the type of infection for less is clearly necessary for urinary tract infections than for meningitis An effective loading dose should be maintained by a slightly smaller dose at intervals of 4 to 6 hours for about 5 days In a virulent infection the first oral

dose may be accompanied by an initial intravenous injection to obtain a rapid therapeutic concentration through the tissues

PENICILLIN

Fleming succinctly described the story of penicillin as four dis tinct chapters Following his classical observation in 1929 of the antibacterial properties of the mould there was a hiatus until 1940-1 when Florey Chain and their colleagues introduced penicillin into clinical medicine (Table 2) This was soon to be followed in 1943 by its mass production and the fourth unfinished chapter is the develop ment of new salts and compounds designed to improve its already high therapeutic activity The present large scale production by submerged aerobic culture of the moulds Penicillium notatum and Penicillium chrysogenum provides approximately 300 tons of pure benzylpenicillin annually for the world market

Antimicrobial range

The bactericidal effect of penicillin is principally against actively dividing as distinct from resting organisms and its range includes the Gram positive bacteria the Gram negative cocci the spirochaetes and Actinomyces israeli

Indications

Penicillin continues to be the most widely used antibiotic because its bactericidal potency is allied with relative freedom from toxic sequelae It is the antibiotic of choice in the first instance for infections due to all the above groups of organisms There are but few exceptions to this generalisation so it is easier to define when it is not used than when it is indicated Hospital strains of Staph aureus are often resistant to its action and the use of another anti biotic may be essential In the treatment of diphtheria it does not of course replace the use of antitoxin and erythromycin is often preferred to penicillin for suppressing further growth of organisms Finally it must be emphasised that sulphonamides are preferable to penicillin in the early treatment of meningococcal meningitis because penicillin crosses the blood brain barrier with less certainty Other than these three instances it should always be the drug of choice for the Gram positive bacteria and Gram negative cocci In addition it is widely used in practice for minor medical and surgical infections on clinical grounds and without preliminary bacteriological identi

TABLE 2—HISTORICAL BACKGROUND TO CHEMOTHERAPEUTIC AGENTS

Agent	Source	Mode of action	Cross resistance with	Introduced by	Year	Reference
Sulphonamides	Synthetic	Bacteriostatic	Other members of the group	Domagk	1935	*Dtsch med Wschr* **61** 250 829
Tyrothricin	Bacillus brevis	Bactericidal		Dubos	1939	*J exp Med* **70**: 1
Penicillin	Penicillium notatum	Bactericidal		Fleming Chain Florey Gardner Heatley Jennings Orr Ewing Saunders	1929 1940	*Brit J exp Path* **10** 226 *Lancet* **2** 226
Streptomycin	Streptomyces griseus	Bactericidal	Dihydrostreptomycin Neomycin	Schatz Bugie Waksman	1944	*Proc Soc exp Biol N Y* **55**: 66
Bacitracin	Bacillus subtilis (B licheniformis)	Bactericidal		Johnson Anker Meleney	1945	*Science* **102** 376
Para aminosalicylic acid (P A S)	Synthetic	Tuberculostatic		Lehmann	1946	*Lancet* **1**: 15
Polymyxin	Bacillus polymyxa	Bactericidal		Benedict Langlykke Stansly Shepherd White Ainsworth Brown Brownlee	1947 1947 1947	*J Bact* **54** 24 *Bull Johns Hopk Hosp* **81**: 43 *Nature* **160** 263
Chloramphenicol	Streptomyces venezuelae Now synthetic	Bacteriostatic		Ehrlich Bartz, Smith Joslyn Burkholder	1947	*Science* **106**: 417
Chlortetracycline	Streptomyces aureofaciens	Bacteriostatic	Other tetracyclines	Duggar	1948	*Ann N Y Acad Sci* **51**: 177
Neomycin	Streptomyces fradiae	Bactericidal	Streptomycin	Waksman Lechevalier	1949	*Science* **109** 305
Fumagillin	Aspergillus fumigatus	Amoebicidal		Hanson Eble	1949	*J Bact* **58**: 527

Oxytetracycline	Streptomyces rimosus	Bacteriostatic	Other tetracyclines	Finlay Hobby P an Regna Routien Seeley Shull Sobin Solomons Vinson Kane	1950	*Science* **111**: 85
Nystatin	St ptomyces noursei	Anti fungal		Hazen Brown	1951	*Proc Soc exp Biol N Y* **76** 93
Erythromycin	Streptomyces erythreus	Bacteriostatic	Carbomycin Spiramycin Oleandomycin	McGuire Bunch, Anderson Boaz Flynn, Powell Smith	1952	*Antibiot and Chemother* **2**: 281
Carbomycin	Streptomyces halstedii	Bacteriostatic	Erythromycin Spiramycin Oleandomycin	Tanner English Lees Routien	1952	*Antibiot and Chemother* **2** 441
Isoniazid	Synthetic	Anti mycobacterial		Grunberg Schnitzer	1952	*Quart Bull Sea View Hosp* **13** 3
Tetracycline	Synthesised from chlortetracycline and oxytetracycline	Bacteriostatic	Other tetracyclines	Boothe, Morton Petisi Wilkinson Williams Conover Moreland English Stephens Pilgrim	1953 1953	*J Amer chem Soc* **75** 4621 *J Amer chem Soc* **75** 4622
Spiramycin	Streptomyces ambofaciens	Bacteriostatic	Erythromycin Carbomycin Oleandomycin	Pinnert Sindico Ninet Preud homme Cosar	1954	*Antibiot Annual* 1954 55 p 724
Novobiocin	Streptomyces spheroides Streptomyces niveus	Bacteriostatic		Wallick Harris Reagan Ruger Woodruff Welch Wright	1955 1955	*Antibiot Annual* 1955 56 p 909 *Antibiot and Chemother* **5**: 670
Oleandomycin	Streptomyces antibioticus	Bacteriostatic	Erythromycin Carbomycin Spiramycin	Sobin English Celmer	1955	*Antibiot Annual* 1954 55 p 827
Vancomycin	Streptomyces orientalis	Bacteriostatic		Pittenger Brigham	1956	*Antibiot and Chemother* **6**: 642

fication Although this empirical use has been justly criticised the practice flourishes with the counter argument that minor infections have thereby ceased to become major hospital problems

Forms

Benzylpenicillin is the British Pharmacopoeial name for the crystalline sodium and potassium salts of penicillin G

Allylmercaptomethyl penicillin (penicillin O) has similar antibacterial and pharmacological properties but appears to be less toxic It should be regarded as an alternative for patients who are sensitive to benzylpenicillin

Procaine penicillin benethamine penicillin and *benzathine penicillin* are less soluble in water less readily absorbed and provide more persistent blood levels In combination with benzylpenicillin the product has the advantages of both sustained and early high blood levels of penicillin The addition of 2 per cent aluminium monostearate to procaine penicillin delays absorption still further In choosing one of the many combinations on the market it is preferable to use a product in which the largest amounts of both long acting and crystalline penicillin are available in the smallest injectable volume

Penethamate hydriodide (*Estopen*) is a penicillin ester, benzyl penicillin diethylaminoethyl ester hydriodide It is slowly absorbed because it is only sparingly soluble and remains inactive until hydrolysed by body fluids to the free form It is said to be selectively concentrated in lung tissue especially when inflammation is present

Phenoxymethyl penicillin (*penicillin* V) is acid resistant but readily soluble in an alkaline medium After oral administration it passes unchanged through the stomach and is absorbed in the alkaline small intestine It is chosen for oral administration when there are good reasons for not giving intramuscular penicillin

Dosage (Tables 3 and 4)

Most susceptible acute infections are controlled by a combination of 600 000 units of procaine penicillin with 400,000 units of crystal line benzylpenicillin in single daily injections continued for five to seven days A larger dose for longer periods is desirable in more prolonged infections including subacute bacterial endocarditis syphilis and actinomycosis

Benzylpenicillin should be given alone for intrathecal or intra pleural administration or when prepared for topical use

Penicillin V is available as 60 mg and 120 mg tablets and an adult dose is 180 mg four hourly One 60 mg tablet is roughly equivalent to 100 000 units of penicillin G The calcium salt is said to produce the highest serum levels

STREPTOMYCIN

This antibiotic was isolated by Schatz Bugie and Waksman (1944) from Streptomyces griseus (Table 2)

Antimicrobial range

It is bactericidal to some Gram positive cocci and to Gram negative bacteria particularly in an alkaline medium Its major value however is due to its activity against Mycobacterium tuberculosis and this is potentiated by the simultaneous activity of isoniazid or para aminosalicylic acid (P A S) which delay the emergence of resistant organisms

Indications

1 In the treatment of all forms of tuberculosis its use should be integrated with other general hygienic measures and any surgical procedures which may be indicated in the course of the disease Streptomycin should never be given without isoniazid or P A S
2 It is combined with penicillin for infections due to Str viridans and Str faecalis notably subacute bacterial endocarditis This combined use may be necessary when there is no clear cut response to penicillin alone because of a partially penicillin resistant organism
3 It may be given with tetracycline for the treatment of brucellosis
4 It is given with a sulphonamide as an alternative form of treatment of plague H influenzae Shigella and coliform infections
5 Intestinal absorption is insignificant and streptomycin is sometimes given orally before bowel surgery for its effect on the intestinal flora The rapid emergence of resistant strains makes it of little value for prolonged use in intestinal infections

Forms

It is available as a stable hydrochloride sulphate and calcium chloride complex for intramuscular use The calcium chloride form which is incompatible with the sulphate is no longer in demand The sulphate is used intrathecally and intrapleurally and very rarely by drip infusion

Dosage (Tables 3 and 4)

When used against the slowly growing tubercle bacilli a single 1 g daily intramuscular injection is sufficiently frequent, and, in fact, some authorities recommend an even less frequent dosage schedule It should be continued for three to six months In contrast, infections due to more rapidly growing non tuberculous organisms demand frequent injections preferably 1 g every eight hours for five days, if control of infection is to be achieved without the development of bacterial resistance In subacute bacterial endocarditis and brucellosis 2 g streptomycin is given daily in divided doses for two to four weeks The intrathecal dose of streptomycin is 2 mg /kg or 100 mg for an adult

Dihydrostreptomycin was produced by catalytic hydrogenation of streptomycin and its sulphate became available for clinical use Since the antimicrobial spectrum is the same as streptomycin, only two advantages could be anticipated It might be effective against streptomycin resistant organisms and it might be less toxic Unfortunately cross resistance between the two antibiotics is so close that dihydrostreptomycin is virtually useless as an alternative Furthermore its toxicity is of a more sinister nature than that of streptomycin since it may cause irreversible deafness with little premonitory warning There is no means of compensating for this disability whereas the vestibular dysfunction following streptomycin may eventually improve and the vertigo and ataxia are partially compensated by visual and proprioceptive reflexes

In condemning dihydrostreptomycin a warning can also be made against the marketed mixtures of streptomycin and dihydrostreptomycin These combine the hazards of both antibiotics The appearance of other anti tuberculous drugs has removed any possible indications for their combined use

THE TETRACYCLINES

In 1948 chlortetracycline was isolated from Streptomyces aureofaciens in the Lederle Laboratories and in 1950 oxytetracycline from Streptomyces rimosus in the Pfizer Laboratories (Table 2) These were the results of much painstaking investigation and *it is to the* credit of these firms that in 1953 they subsequently produced the basic analogue tetracycline

These three antibiotics are so similar that their pharmacological

and antibacterial properties dosage and complications can for practical purposes be discussed under a common heading Indeed it is this close chemical similarity which robs them of the virtue of therapeutic distinctiveness To provide fresh therapeutic vigour in antibacterial warfare newly introduced antibiotics should be chemically different if they are to be effective Analogues of currently used antibiotics have so far provided the same disadvantage as the prototype with but few advantages

Antimicrobial range

The tetracyclines are bacteriostatic against most Gram positive and Gram negative bacteria the spirochaetes all rickettsiae and against the small group of psittacosis lymphogranuloma viruses

Indications

The indications for using tetracycline may be broadly grouped as follows

1 An alternative to penicillin for Gram positive and spirochaetal infections and in actinomycosis
2 An alternative to streptomycin for Gram negative infections
3 All rickettsial infections
4 Virus infections—psittacosis lymphogranuloma venereum trachoma inclusion conjunctivitis
5 Pneumonia associated with raised cold haemagglutinins
6 Acute or relapsing amoebic dysentery in conjunction with amoebicidal agents
7 Prolonged treatment of brucellosis

Forms

Tetracycline is available as 50 mg 0 1 g and 0 25 g tablets and capsules One teaspoonful of a suspension is approximately equivalent to 0 25 g of tetracycline hydrochloride but there are also flavoured syrups and paediatric drops of varying strength There are preparations for intramuscular and intravenous use and the form used for intravenous injection may also be given intrapleurally but *not* intrathecally Topical application may be used for eyes ears and skin The eye drops are buffered with borate and the ear drops are prepared with benzocaine in propylene glycol Recent work indicates that oral tetracycline combined with sodium metaphosphate produces higher serum levels than the usual hydrochloride preparation

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Dosage (Tables 3 and 4)

Five to seven days oral treatment is sufficient for most susceptible acute infections, but since tetracycline is only bacteriostatic relapses may demand a longer or a second course For *deep* intramuscular use 0 1 g is combined with 20 mg procaine hydrochloride in 2 ml water and administered eight hourly until tetracycline can be tolerated by mouth If it is necessary to give it intravenously, 0 5 g tetracycline buffered with ascorbic acid as a 2 or 5 per cent solution is freshly prepared each day and administered by drip transfusion twelve hourly or alternatively 0 1 g may be given very slowly in a 1 per cent solution The intravenous preparation is diluted for intrapleural instillation so that 0 25 g is given in 50 to 100 ml sterile saline

CHLORAMPHENICOL

This was isolated from Streptomyces venezuelae in 1947 by Burkholder and his co-workers (Table 2) Its chemical structure was soon recognised and it is now prepared synthetically

Antimicrobial range

It is bacteriostatic against a range of organisms similar to the tetracyclines

Indications

Because of its nitrobenzene ring severe bone marrow depression and fatalities have followed its use Although this is rare compared with the very large number who have benefited from the drug the notoriety has greatly restricted its use If other less toxic antibiotics are equally effective there is no justification for employing it There are three main indications for using chloramphenicol

1 Salmonella infections in the treatment of which it is superior to other agents
2 Influenzal meningitis because chloramphenicol readily diffuses across the blood brain barrier in adequate concentrations and H influenzae is highly sensitive to its action
3 Infections with micro-organisms resistant to all other antibiotics the most notable example being Staph aureus

Forms

Each 0 25 g capsule is roughly equivalent to two teaspoonfuls of the suspension of chloramphenicol palmitate or cinnamate The capsules may be pierced for rectal administration but suppositories

of 0 25 g size are also available It may be given intramuscularly and intravenously but not by intrathecal or intrapleural routes Eye drops (0 5 per cent) in borate buffer and ear drops (10 per cent) in propylene glycol are available

Dosage (Tables 3 and 4)

The average adult oral dose is 0 25 g four hourly for five to seven days The total dose should never exceed 25 g It is only rarely necessary to give it by deep intramuscular or intravenous routes (subcutaneous injection should be avoided) the usual adult dose is then 1 g twelve hourly until it is possible to administer it by mouth Intravenous infusion should be in the form of a 0 5 per cent solution in saline or 5 per cent dextrose given at a rate not exceeding 2 ml /minute The special intravenous preparation contains 0 25 g chloramphenicol in each ml of 50 per cent aqueous N N dimethyl acetamide It must be diluted with normal saline before use

ERYTHROMYCIN

This antibiotic was isolated from Streptomyces erythreus (Table 2)

Antimicrobial range

It is a bacteriostatic agent whose antibacterial range of activity is somewhat similar to penicillin namely the Gram positive bacteria Gram negative cocci spirochaetes and Actinomyces israeli In addition it has some effect although this is variable and uncertain against Gram negative bacilli of the Haemophilus group and against the psittacosis group of viruses It is ineffective against enteric bacteria so it is less likely than the tetracyclines to upset the intestinal flora during treatment

Indications

1 It is effective against Corynebacterium diphtheriae and should be given in conjunction with antitoxin for the treatment of diphtheria
2 It is used as an alternative to penicillin in the treatment of infections due to penicillin resistant organisms notably Staph aureus or when allergic reactions preclude the use of penicillin

Forms

It is available in 0 1 g 0 2 g and 0 25 g tablets One teaspoonful of erythromycin stearate or the paediatric suspension in ethyl

carbonate contains 0 1 g in 5 ml For intramuscular use, erythro mycin lactobionate is diluted with water or 5 per cent dextrose in a strength of 50 mg /ml (5 per cent) or for intravenous use in a strength of 1 per cent with saline or 5 per cent dextrose There is also a 1 per cent ointment for topical use

Dosage (Tables 3 and 4)

The adult oral dose of 0 25 g six hourly is continued for five to seven days If it is not tolerable by mouth, 0 5 g is given by intra venous infusion daily until oral therapy is practicable

CARBOMYCIN

Carbomycin was isolated from Streptomyces halstedii (Table 2) It closely resembles erythromycin in its pharmacological properties and bacteriostatic activity but since its effect is inferior to erythromycin the tetracyclines and chloramphenicol there are no obvious indications for its use

SPIRAMYCIN

This antibiotic was isolated from Streptomyces ambofaciens obtained from French soil (Table 2) Its antibacterial range of activity is similar to erythromycin with which it shares some degree of cross resistance In view of this close similarity with erythromycin (and also to carbomycin) there is no clear cut indication for using spiramycin in preference to erythromycin It was hoped that it might have superior anti staphylococcal activity but these organisms rapidly become resistant to it and the concurrent use of novobiocin does not minimise the development of resistance The recommended daily oral dosage of spiramycin is 100 mg /kg for an adult 2 g is given initially and followed by 1 g six hourly Its toxicity is of the same low order as erythromycin

BACITRACIN

The culture filtrate of a strain of Bacillus subtilis isolated from a patient named Tracy was the source of this polypeptide antibiotic (Table 2) Its bactericidal range fate in the body and development of bacterial resistance are similar to penicillin but nephrotoxicity has restricted its use Fortunately it is not inactivated by blood or tissue exudates so it is suitable for topical applications Bacitracin and penicillin have a synergistic action and they are often used together for this reason

TABLE 3 —DOSAGE

Chemotherapeutic agent	Route	Dose mg /kg /24 hours	Normal adult dose grammes		Frequency
			Loading	Continuation	
Sulphonamides	Oral	100-200	3	1 2	3 to 6-hourly
Penicillin V Benzylpenicillin Procaine penicillin	Oral 1 m 1 m		180 mg 400 000 units 600 000 units	180 mg 600 000 1 200 000 units	4 hourly Daily
Tetracycline	Oral	15	1	0 25	6 hourly
Chloramphenicol	Oral	50-100	2	0 25	6-hourly
Streptomycin	1 m	20-40	1	1	Daily or 8 hourly
Erythromycin } Oleandomycin }	Oral	30-50	1	0 25	6 hourly
Polymyxin	1 m Oral	1 2 8 16	25 mg 0 2	25 mg 0 1	6-hourly 4 hourly
Bacitracin	1 m *Oral*	1 000 units/kg *5 000 units/kg*	20 000 units 50 000 units	10 000-20 000 units 50 000 units	6-hourly 4 hourly
Neomycin	Oral	100	1	1	4 hourly
Novobiocin	Oral	15 30	1	0 5	6 hourly
Vancomycin	1 v	15 30	0 5	0 5	6-hourly
Nystatin	Oral	50 000 units/kg	1 000 000 units	500 000 units	6-hourly
Isoniazid	Oral	3 8	0 1	0 1	Twice daily
Sodium P A S	Oral	250	3	3	4 to 6 hourly

1 m =intramuscular   1 v =intravenous

Table 4 —Routes of Administration

Drug	Oral	Intramuscular	Intravenous	Intrathecal Intrapleural	Ointment	Eye drops Ear drops	Other
Sulphonamides	Tablet 0 5 g	Thiasolucin 20 / Sulphafurazole 40		—	Na sulphacetamide 6 % Sulphafurazole 4 % Sulphathiazole 10%	Na sulphacetamide 10 30 % Sulphafurazole 4 /	Powder Nasal spray Na sulphacetamide 7 5 % with ephedrine 1 /
Penicillin	Penicillin V tablet 60 and 120 mg Also suspension	Soluble and long acting	Rarely necessary Benzylpenicillin with heparin by infusion	Benzylpenicillin 20 000 units	Benzylpenicillin 1 000 2 000 and 25 000 units/g	Benzylpenicillin Eye—2 000 units/ml Ear—6 000 units/ml	Nose—6 000 units /ml with ephedrine 1 000 units lozenge
Tetracycline	Tablet 50 mg 0 1 g 0 25 g Syrup suspension Paediatric drops	5 / solution with procaine	0 5 g in drip infusion 12 hourly	Never intrathecal Intrapleural 0 25 g in 0 5% solution	3 / Eyes—0 5% and 1 /	0 5%	Lozenge 15 mg
Chloramphenicol	Capsule 0 25 g Suspension *of palmitate or cinnamate*	Rarely necessary *1 g 12 hourly*		—	1 /	Eye—0 5 % Ear—10 %	Suppository 0 25 g Subconjunctival suspension 15 / Dusting powder 5 %
Streptomycin	Not absorbed Sulphate powder readily soluble	Sulphate or hydrochloride	Rarely necessary 1 g /litre/ 24 hours	Sulphate Intrathecal 0 1 g Intrapleural 1 g	0 5 %	—	—
Erythromycin	Stearate Tablet 0 1 g 0 2 g 0 25 g Paediatric suspension	5 / Dilute with water or 5 / dextrose	Lactobionate 1 / Dilute with saline or dextrose solution	—	1 /	—	—

Polymyxin	Sulphate Not absorbed Tablet 25 and 50 mg	With procaine Change injection site frequently	Slow infusion 1 g /250 ml /24 hours	Omit procaine Adult 5 10 mg Child 2 5 mg	0·1 % Also combined with bacitracin	Ear—0·1 %	Subconjunctival suspension 5 % with mydricaine Nasal 0·5 %
Bacitracin	Not absorbed Tablet 50 000 units	Rarely necessary	—	Solution 500-1 000 units/ml 5 10 ml omit procaine	500 units/g Also combined with polymyxin	500 units/ml	—
Neomycin	Sulphate Not absorbed Tablet 0·5 g	—	—	Never intrathecal Pleura joints— 0·25 g in 5 ml Peritoneum— 0·5 g in 250 ml	0·5 % Also combined with gramicidin	—	Lotion 0·5 %
Novobiocin	Tablet or capsule 0·125 g 0·25 g	0·25 g 8 hourly	0·5 g 12 hourly	—	—	—	Combined with penicillin
Vancomycin	Not absorbed Tablet 0·5 g	—	0·5 g 6 hourly	—	—	—	—
Oleandomycin	Capsule 0·1 g 0·25 g	—	—	—	—	—	Combined with tetracycline
Nystatin	Tablet 500 000 units	—	—	—	100 000 units/g	—	Vaginal tablet 100 000 units
Isoniazid	Tablet 50 mg 0·1 g 0·2 g 0·25 g Syrup	Rarely necessary Ampoule available containing 50 mg /2 ml	Rarely necessary Ampoule available containing 50 mg /2 ml	Rarely necessary Ampoule available containing 50 mg /2 ml	—	—	Combined with Na P A S
Sodium P A S	Sugar coated tablet Cachet dragee granules powder of various strengths	—	Rarely necessary 5 10 % solution 10 g in 125 ml saline	Rarely necessary 5 10 % solution Intrathecal 10 ml 5 % solution Intrapleural 20 ml 20 % solution	—	20 %	Combined with isoniazid

Antimicrobial range

It is bactericidal to the Gram positive cocci, the clostridial group and to spirochaetes

Indications

1 It is poorly absorbed from the gut and nephrotoxicity can be discounted when it is given by mouth Bacitracin can be expected to eliminate clostridia and faecal streptococci from the intestinal flora Since the Gram negative bacilli remain unaffected the insensitive coliform organisms will prevent the emergence of yeasts so troublesome moniliasis is not a complication By this route it may be given as a pre operative cover for bowel surgery or as a less effective alternative to the tetracyclines for controlling secondary infection in intestinal amoebiasis It has a synergistic action with streptomycin and the pair can be expected to eliminate both Gram positive and Gram negative bacteria within the gut
2 Topical use is popular because there is no danger of nephro toxicity nor do local sensitisation reactions occur It is valuable locally in the treatment of gas gangrene because clostridia are sensitive to its action but this should of course be in addition to surgical debridement and antitoxin Bacitracin may also be given by intrathecal intracisternal or intraventricular routes for meningitis brain abscess chronic osteomyelitis of the skull or post traumatic infections if due to Gram positive organisms particularly staphylococci which may be resistant to other more frequently used antibiotics Its local use also includes the con junctiva pleura, pericardium peritoneum joints ears and nasal sinuses
3 The only present indication for its systemic use is a grave infection due to Staph aureus resistant to all other anti staphy lococcal agents Under these circumstances the life saving value of bacitracin overrides the risk of nephrotoxicity

Forms

Each tablet for oral use contains 10 000 units of bacitracin Solutions for instillation into serous cavities or for surface applica tion should be in a strength of 500 to 1 000 units/ml and ointments contain 500 units/g base There is a marketed ointment which combines bacitracin and polymyxin and another which contains bacitracin polymyxin and neomycin

Dosage (Tables 3 and 4)

An average adult oral dose is 50 000 units (5 tablets) four hourly for three days For instillation into serous cavities 5 to 10 ml containing 500 to 1 000 units/ml may be given twelve hourly Surface applications such as to the conjunctiva ears or nasal sinuses may be given three hourly Bacitracin solution does not penetrate the intact cornea When it is necessary to give it by the intramuscular route the usual adult dose is 10 000 to 20 000 units six hourly

POLYMYXIN

The polymyxins A B C D and E are polypeptides isolated independently in Great Britain and in the United States from Bacillus polymyxa (Table 2) Polymyxin was originally known as aerosporin Only polymyxin B and E are sufficiently non toxic for clinical use in Britain polymyxin B sulphate is commercially available

Antimicrobial range

Its bactericidal range is limited to the Gram-negative bacilli comprising the Haemophilus Brucella and particularly the coliform groups It is not effective against Proteus nor against the Gram negative cocci

Indications

Nephrotoxicity although insignificant with current preparations has limited its use to the following conditions

1 Pseudomonas pyocyanea (aeruginosa) infections for which it is the drug of choice This includes infections of the meninges or other serous surfaces eyes ears urinary tract and wounds
2 Polymyxin is not absorbed from the gut By this route it suppresses Gram negative bacilli in the intestine and must be considered in bowel infections which do not respond to the sulphonamides streptomycin or neomycin It has been used to treat carriers of Shigella Since it does not affect the Gram positive intestinal flora monilia and other fungi do not emerge as dominants

Forms

Polymyxin tablets of 25 mg and 50 mg strength are available for oral use It may also be given intravenously and by intramuscular

Antimicrobial range

It is bactericidal to the Gram positive cocci the clostridial group and to spirochaetes

Indications

1 It is poorly absorbed from the gut and nephrotoxicity can be discounted when it is given by mouth Bacitracin can be expected to eliminate clostridia and faecal streptococci from the intestinal flora Since the Gram negative bacilli remain unaffected the insensitive coliform organisms will prevent the emergence of yeasts so trouble ome moniliasis is not a complication By this route it may be given as a pre-operative cover for bowel surgery or as a less effective alternative to the tetracyclines for controlling secondary infection in intestinal amoebiasis It has a synergistic action with streptomycin and the pair can be expected to eliminate both Gram positive and Gram negative bacteria within the gut
2 Topical use is popular because there is no danger of nephrotoxicity nor do local sensitisation reactions occur It is valuable locally in the treatment of gas gangrene because clostridia are sensitive to its action but this should of course be in addition to surgical debridement and antitoxin Bacitracin may also be given by intrathecal intracisternal or intraventricular routes for meningitis brain abscess chronic osteomyelitis of the skull or post traumatic infections if due to Gram positive organisms particularly staphylococci which may be resistant to other more frequently used antibiotics Its local use also includes the con junctiva pleura pericardium peritoneum joints ears and nasal sinuses
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Indications

Nephrotoxicity and deafness have confined its uses to oral and topical administration

1 By mouth it is often combined with a non absorbable sulphonamide to prepare the bowel before intestinal surgery In the same way it is useful in intestinal amoebiasis because it suppresses secondary bacterial contaminants It is probably the best antibiotic for the treatment of hepatic coma in which intestinal organisms including those which produce ammonia contribute to toxaemia and to a syndrome of portal systemic encephalopathy (impending hepatic coma) Patients with hepatic cirrhosis and chronic portal systemic encephalopathy may need to take oral neomycin in interrupted courses for several months
2 It may be counted amongst the anti staphylococcal agents which are of use in the treatment of staphylococcal enteritis
3 It may be used in the forms of a solution or ointment for the local treatment of wounds or burns contaminated by a mixed group of organisms such as Staph aureus and Proteus For the same reason it may be instilled into serous cavities at the same time as a less toxic antibiotic such as penicillin or streptomycin is being used parenterally Additive action may be expected with any of these combinations

Forms

Each tablet for oral use contains 0 5 g neomycin sulphate Solutions of various strength may be instilled into the pleura peritoneum or joint cavities and skin lotions and ointments are available (Table 4)

Dosage (Tables 3 and 4)

An adult oral dose of 1 g four hourly is given for two days pre operatively for seven days in established intestinal infections or for prolonged periods in incipient hepatic coma A dose of 0 25 g in 5 ml sterile saline may be instilled into the pleura or joint cavity daily and 0 5 g neomycin in 250 ml saline may be irrigated into the peritoneum daily for three days

NOVOBIOCIN

Novobiocin has also been called streptonivicin albamycin cathomycin and cardelmycin It should not be confused with the

intrathecal and intrapleural routes There are various topical preparations and a solution containing 1 to 5 mg /ml may be used to irrigate sinus tracts

Dosage (Tables 3 and 4)

1 mg of polymyxin is equivalent to 10 000 units An average adult dose is 25 mg six hourly by the intramuscular route or 0 1 g four hourly by mouth for five days When given intravenously an adult dose of 0 1 g may be given by slow infusion in 250 ml of 5 per cent dextrose daily In the treatment of meningitis its intramuscular use should be reinforced by the daily intrathecal administration in saline of 5 mg for adults or 2 mg for children Similar doses may be used for instillation into other serous cavities For ophthalmic infections 0 1 per cent solution or ointment may be combined with an initial subconjunctival injection of 0 25 ml containing 3 to 5 mg

TYROTHRICIN

This was the first antibiotic to be employed clinically following its isolation by Dubos in 1939 from Bacillus brevis (Table 2) It is a mixture of two polypeptides gramicidin (20 per cent) and tyrocidine (80 per cent) Its bactericidal action is principally against Gram positive organisms which are particularly susceptible to gramicidin

There is no present clinical indication for its use Parenterally it may cause severe haemolysis orally it is inactivated by gastric juice topically it has caused chemical irritation and wound bleeding and anosmia has followed its use as nasal drops

NEOMYCIN

In 1949 Waksman and Lechevalier reported the isolation of this antibiotic from the culture filtrate of Streptomyces fradiae (Table 2)

Antimicrobial range

It is a bactericidal agent with a wide range of activity against the Gram negative bacteria particularly the enteric group Brucella Pasteurella and cholera vibrio but only to a variable or insignificant degree against the Haemophilus group and Neisseriae The Gram positive organisms have significant variations in susceptibility but Staph aureus C diphtheriae Myco tuberculosis and B anthracis often contain sensitive species Neomycin may be effective against certain strains of spirochaetes and actinomycetes

Sigmamycin

Sigmamycin is a marketed combination of oleandomycin (83 mg) with tetracycline (167 mg) in capsule form The combination is intended to be synergistic, so that bacterial resistance to either may be minimised The recommended adult oral dose is one or two capsules (0 25 to 0 5 g) six hourly for five to seven days (Table 3)

NYSTATIN

This anti fungal agent, derived from Streptomyces noursei has also been called fungicidin and mycostatin (Table 2) It has marked in vitro activity against numerous fungi and yeasts but not against bacteria In clinical practice its main value at present is in the treatment of Candida (Monilia) albicans infections which are particularly liable to follow prolonged broad spectrum antibiotic therapy When given by mouth in doses of 500 000 to 1 000 000 units six hourly gastrointestinal absorption is very poor so its action is confined to the intestinal flora Its simultaneous administration with tetracycline considerably lessens the yeast flora of the gastrointestinal tract and this combination should be used when tetracycline must be administered orally for prolonged periods It may also be given in the form of 100 000 unit vaginal tablets or as an ointment containing 100 000 units/g base for the treatment of monilial vaginitis This treatment is superior to and also far less troublesome than that involving dyes such as gentian violet

VANCOMYCIN

This antibiotic was isolated from Streptomyces orientalis which was found in soil samples from Borneo and India (Table 2) Vancomycin hydrochloride is a white solid very soluble in water and relatively stable

Antimicrobial range

It is bactericidal to all Gram positive cocci and to one Gram negative coccus N gonorrhoeae

Indications

Like novobiocin and oleandomycin its main value is in the treatment of staphylococcal infections when other antibiotics have failed However unlike them it is not absorbed following oral administration, so that although oral administration is satisfactory

apparently dissimilar Russian antibiotic albomycin It has been isolated from Streptomyces niveus and Streptomyces spheroides as a dibasic acid and is made available as the sodium or calcium salt

Antimicrobial range

Novobiocin is effective against Gram positive cocci but ineffective against Gram negative organisms with the exception of Proteus which shows moderate in vitro sensitivity and neisseria

Indications

Its main value at present is in the treatment of staphylococcal infections when other antibiotics have failed It is probable that its combined action with another anti staphylococcal agent such as erythromycin or tetracycline will prove the most effective way of delaying the emergence of antibiotic resistant hospital strains of Staph aureus

Forms

Each capsule contains 0 25 g of novobiocin for oral use and it may also be given intramuscularly and intravenously In vitro studies show that it is inactivated by the presence of human serum and that it is more effective at a *p*H of 5 5 than 8 1

Dosage (Tables 3 and 4)

A dose of 0 5 g novobiocin should be given by mouth six hourly for five days If this is impracticable the same dose may be given intravenously every twelve hours or 0 25 g intramuscularly eight hourly until it is possible to give it by mouth

OLEANDOMYCIN

This antibiotic was isolated from Streptomyces antibioticus (Table 2) Its bacteriostatic range of activity parallels erythromycin carbomycin and spiramycin The main indication for its use appears to be as an alternative to or in combination with other antibiotics in the control of staphylococcal infections Cross resistance may limit this value but a large selection of anti staphylococcal agents is welcomed to allow judicious ringing the-changes of various antibiotics in an effort to maintain control over resistant organisms The usual adult oral dose is 0 25 to 0 5 g six hourly for five to seven days (Table 3)

intramuscular or intrathecal routes Mixtures containing isoniazid and sodium P A S are also commercially available in cachets of several different strengths The quantity of isoniazid in each cachet may be 12 5 mg 17 mg 25 mg 33 mg 33 3 mg or 50 mg It is also mixed with the calcium salt of benzoylamino-hydroxybenzoic acid (B P A S) as a cachet containing 25 mg isoniazid and as a powder containing 87 5 mg isoniazid Finally isoniazid has been chemically combined with para aminosalicylate in the form of a 0 1 g tablet containing 47 per cent isoniazid and 53 per cent P A S ('dipasic)

Dosage (Tables 3 and 4)

The usual adult oral dose is 0 2 g to 0 3 g daily for six to twelve months This is administered twelve hourly when the isoniazid is used alone but when mixed with sodium P A S the combination is prescribed four hourly The chemically combined dipasic is given in a dose of 11 mg /kg daily which gives an adequate dose of isoniazid

PARA AMINOSALICYLIC ACID (P A S)

In 1946 Lehmann demonstrated the in vitro tuberculostatic action of P A S on bovine strains of Myco tuberculosis (B C G) and also reported early but encouraging clinical results in a group of Swedish patients (Table 2) Its value in the chemotherapy of tuberculosis has now been established

Antimicrobial range

Its bacteriostatic action is specific for Myco tuberculosis and almost entirely on virulent human strains

Indications

The tuberculostatic action of P A S alone is inferior to streptomycin or isoniazid Its main value lies in its synergistic action with streptomycin or isoniazid in delaying the rate of development of resistant tubercle bacilli to any of these three agents It is therefore combined with streptomycin or isoniazid or both during courses of treatment of all types of tuberculosis

Forms

The salts cause less gastric irritation than the free acid and are less likely to lead to acidosis with prolonged use Sodium or calcium

for staphylococcal enterocolitis intravenous administration is essential if there is septicaemia or extra intestinal lesions

Forms

Vancomycin hydrochloride is available as tablets for oral use and as a solution for intravenous administration

Dosage (Tables 3 and 4)

A dose of 0 5 g is given to adults six hourly by either oral or intravenous routes

ISONIAZID

Isoniazid is the hydrazide of isonicotinic acid and it is readily synthesised Demonstration of its anti tuberculous activity in mice by Grunberg and Schnitzer in 1952 led to clinical trials which quickly confirmed its therapeutic value in human tuberculosis

Antimicrobial range

It is active against mycobacteria and of these principally Myco tuberculosis Isoniazid appears to be bactericidal to growing organisms which lose their acid fast staining characteristics under its influence Unlike streptomycin it is able to reach and affect intracellular organisms

Indications

It is one of the most effective agents in the treatment of all forms of tuberculosis Since it diffuses freely throughout the body isoniazid is particularly useful in tuberculosis of serous surfaces Its oral administration may render intrathecal streptomycin superfluous for the treatment of tuberculous meningitis Its other great advantage is that there is no cross re istance between it and streptomycin or para aminosalicylic acid (P A S) However bacterial resistance rapidly follows it use alone so it should always be given in combina tion with streptomycin or P A S to delay the emergence of resistant tubercle bacilli

Forms

Isoniazid is available as 50 mg 0 1 g 0 2 g and 0 25 g tablets and a syrup containing 20 mg per teaspoonful Its free diffusibility makes routes other than by mouth unnecessary although ampoules (50 mg in 2 ml) are available for administration by intravenous

CHAPTER 2

FATE AND MODE OF ACTION

FATE IN THE BODY

THE absorption excretion blood and tissue concentrations are of importance in selecting the most suitable agent for a particular purpose and in deciding the route of administration Although parenteral administration will provide higher blood levels and hence more significant tissue diffusion many of the chemotherapeutic agents are more conveniently given by mouth and some of them are only safe by this route Table 5 shows the distribution of the substance in various body fluids when it is given by the usual route employed in clinical practice The sulphonamides have an unabsorbable form which is of course not included as when given orally it does not reach the body fluids Forms of penicillin having different rates of absorption are too numerous to be detailed and the original benzylpenicillin is considered as a prototype

Absorption and peak blood levels

When given by the recommended route the peak level of the agents tabulated is within six hours These substances should therefore be administered at four to six hour intervals This maintains adequate therapeutic levels and prevents the emergence of resistant bacteria Depot forms of penicillin may be used to maintain adequate levels by only one daily injection

Streptomycin is another antibiotic usually given parenterally is also short acting but has no depot form If used against non tuberculous infections repeated daily injections are inevitable The tubercle bacillus grows slowly and once daily injections of streptomycin are adequate in the treatment of tuberculosis

Plasma protein binding

After absorption sulphonamides and antibiotics are partly bound to plasma albumin The bound fraction is not antibacterial some natural penicillins such as penicillin K are bound to such a degree that their bactericidal activity is greatly reduced With the drugs in common use the linkage is presumably a loose one since they are readily detected in the urine within twenty four hours of adminis

para aminosalicylate is therefore usually prescribed Sodium P A S is available as enteric coated tablets cachets dragees granules and powder for oral use Confusion is liable to arise whether the dose is expressed in terms of the free acid or its sodium salt Some manufacturers endeavour to overcome this confusion by issuing tablets containing both 0 5 g and 0 69 g sodium P A S, and packages of powder containing 4 1 g sodium P A S (≡3 g P A S) or 5 g sodium P A S In this way the pharmacist is able to meet the requirements of physicians who prescribe in terms of the free acid or of the sodium or calcium salts Since the salt is far more popular than the free acid nowadays it is advisable to think in terms of the salt and to remember that this entails a conversion factor 0 5 g P A S ≡0 69 g sodium P A S or 0 67 g calcium P A S This difficulty will undoubtedly be overcome in the future by pharmaceutical standardisation

Cachets contain 1 g 1 5 g and - g sodium P A S dragees contain 0 69 g sodium P A S and there are granules which contain half their own weight of sodium P A S (one special supplied measure carries 4 g of granules ≡2 g sodium P A S) There are also cachets in which 1 25 g or 1 5 g sodium P A S is already mixed with various doses of isoniazid Finally calcium 4 benzamido salicylate (1 g cachets) are available alone or with isoniazid When broken down in the body it liberates about half its weight of P A S Parenteral forms of sodium P A S are available but rarely indicated

Dosage (Tables 3 and 4)

Since the dosage of P A S lies within the wide limits of 12 g to 20 g by mouth daily there is fortunately little risk attached to the above confusion of dose values The average adult dose is 12 g of the acid or 15 g of the salt It may be given in a daily dose of 10 g of a 5 to 10 per cent solution intravenously 10 ml of a 5 per cent solution intrathecally 20 ml of a 20 per cent solution intrapleurally or as a 20 per cent solution to the ears

Serous cavities

The sulphonamides and antibiotics diffuse reasonably well into the pleural peritoneal and synovial cavities but in concentrations which are about one quarter to one half the blood level Thick avascular tissue prevents diffusion to the site of infection when a high local concentration of the agent is desirable it should be instilled directly into the serous cavity For Gram positive organisms soluble benzylpenicillin may be given in doses of 50 000 units daily or alternatively bacitracin 10 000 units A Gram negative infection may demand tetracycline up to 1 g of the intravenous preparation in a concentration of 1 to 5 mg /ml may be used intrapleurally Streptomycin (up to 1 g) or polymyxin (5 to 10 mg) in saline may also be used against Gram negative organisms

These measures are of course supplementary to surgical drainage and possible enzymatic debridement with intrapleural trypsin which digests protein or streptokinase streptodornase which breaks down fibrin clots Because of its diffusibility oral isoniazid should always be used for pleural tuberculosis

Bile

The drugs may diffuse passively into the bile or they may be concentrated by many times the blood level in the hepato biliary system and selectively excreted by this route (Table 5) In the presence of hepatic cell dysfunction there is some retention of the antibiotic and higher blood levels can be expected This holds particularly for carbomycin which is excreted in bile in concentration approaching 200 times the blood level

MODE OF ACTION

Although the precise mode of action of chemotherapeutic agents is ill understood it seems probable that they enter into and thereby interfere with various specific metabolic processes necessary for growth and survival of the organism Although the interfering drug must be structurally similar to the metabolite it has of course to be sufficiently unrelated to be devoid of essential metabolic activity otherwise bacterial metabolism would be uninterrupted In becoming antibiotic resistant or even antibiotic dependent bacteria learn to use a by pass system for their metabolic requirements It has been said that a drug which is incapable of inducing resistance has little chance of being a chemotherapeutic agent

tration The affinity of the plasma protein binding influences the ease of diffusion of the agent and its concentration in body fluids such as the cerebrospinal fluid

Renal excretion

The sulphonamides and antibiotics are principally excreted by glomerular filtration Tubular function is responsible for excretion of 80 per cent of penicillin a variable amount of some of the sulphonamides and of P A S and the inactive degradation products of chloramphenicol With the possible exception of neomycin chemotherapeutic agents achieve therapeutic concentrations in the urine within twelve hours of absorption

In the presence of impaired renal function massive and possibly toxic blood levels may be attained When amyloidosis is suspected to complicate tuberculosis or any other chronic infection or if renal function is considered poor for any reason blood antibiotic levels or failing these blood urea levels may be helpful in controlling the dose

Cerebrospinal fluid

Although drugs penetrate the inflamed meninges more efficiently than the normal blood brain barrier their diffusion is irregular and unreliable The exceptions are the sulphonamides chloramphenicol and isoniazid all of which provide adequate levels in the cerebrospinal fluid following oral administration These agents are therefore indicated for the treatment of meningitis due to susceptible organisms

When given parenterally especially in very large doses there may be effective spinal fluid levels of penicillin and tetracycline However whenever feasible the agent should be given intrathecally in the treatment of meningitis for high local concentration is then independent of the blood brain barrier This is usually supplemented by oral or intramuscular administration The antibiotics which can be instilled by intrathecal intracisternal and intraventricular routes are penicillin streptomycin polymyxin and bacitracin (Table 4)

Placental transmission

The sulphonamides penicillin tetracyclines chloramphenicol isoniazid and streptomycin diffuse into the foetal circulation where they are detectable in about one half the level of that found in the maternal circulation (Table 5)

Sulphonamides compete successfully with para aminobenzoic acid (PABA) which is used by many micro-organisms for the synthesis of folic and folinic acid Bacteria which use this PABA folic acid metabolic chain are sensitive to sulphonamide bacteriostasis but they have been shown to become resistant in vitro when preformed folic acid is supplied to them

Enzyme systems are probably also inhibited by penicillin streptomycin the tetracyclines and other antibiotics although the biochemical evidence for this is scanty and at present amounts only to a large number of apparently unrelated observations

Penicillin interferes with the ability of actively dividing Gram positive bacteria to assimilate glutamic acid a substance which they do not normally synthesise Penicillin re istance can be induced by exposing organisms to gradually increasing amounts of antibiotic so that they become independent of an external source of amino-acids and acquire their own power of synthesis It has been suggested that penicillin interferes with such enzymes as galactosidase and ribonuclease which are essential to nucleic acid metabolism in cells and with the utilisation of glycine in forming peptides

Streptomycin has been shown to interfere with the catalytic action of oxaloacetic acid in pyruvate oxidation It seems therefore that by interfering with the Krebs tricarboxylic acid cycle its anti metabolite action would affect carbohydrates fatty acids and amino-acids

The *tetracyclines* and *chloramphenicol* appear to inhibit protein synthesis at the nucleic acid level Experiments involving both staphylococci and Esch coli show accumulation of nucleic acids in the presence of these antibiotics presumably because successful inhibition prevents further protein synthesis

Isoniazid is structurally similar to pyridoxine and its mode of action is probably based on interference in utilising this vitamin Tubercle bacilli exposed in vitro to isoniazid lose their acid fast staining characteristics and fail to grow even on subculture away from its influence This phenomenon is not observed with streptomycin for organisms which have been removed from the influence of streptomycin resume growth

Para aminosalicylic acid (P A S) is structurally similar to the sulphonamides and to para aminobenzoic acid Mode of action is probably also by competition with PABA

TABLE 5.—DISTRIBUTION IN BODY FLUIDS AFTER USUAL ROUTE OF ADMINISTRATION

Agent	Usual route	Peak blood level (hrs.)	Urinary excretion	C S F	Placental transmission	Serous cavities	Bile
Absorbable sulphonamide	Oral	<3	Rapid	$\times\frac{3}{4}$*	$\times\frac{1}{2}$†	$\times\frac{1}{2}$*	×1*
Benzylpenicillin	i m	1	Rapid	Unsatisfactory	$\times\frac{1}{2}$	$\times\frac{1}{4}$	×5
Tetracyclines	Oral	2 4	Slow	Unsatisfactory	$\times\frac{1}{3}$	$\times\frac{1}{4}$ $\frac{1}{2}$	×10
Chloramphenicol	Oral	<2	Rapid	$\times\frac{1}{2}$	Free diffusion		$\times\frac{1}{2}$
Streptomycin	i m	1 2	Rapid	Unsatisfactory	$\times\frac{1}{4}$ $\frac{1}{2}$	$\times\frac{1}{4}$–$\frac{1}{2}$	$\times\frac{1}{4}$ $\frac{1}{2}$
Erythromycin	Oral	1 4	Rapid	0	Unsatisfactory	Unsatisfactory	×8 64
Polymyxin	i m	2	Slow	0	—	0	0
Bacitracin	Oral	Negligible	0	0	0	0	0
	i m	2	Slow	0	—	Readily detected	—
Neomycin	Oral	Negligible	Negligible	0	0	0	0
Novobiocin	Oral	2	Rapid	0	—	Readily detected	—
Vancomycin	Oral	Negligible	0	0	0	0	0
	i v	Immediate	Rapid	0	0	0	—
Oleandomycin	Oral	4	Rapid	0	0	0	—
Nystatin	Oral	Negligible	0	0	0	0	0
Isoniazid	Oral	1 2	Rapid	Free diffusion throughout body fluids			
Sodium P A S	Oral	1 2	Rapid	Unsatisfactory	0	0	0

* Relation to blood level † Relation to maternal blood level

observed when they are combined with each other When a Group 2 agent is combined with a Group 1 drug the result depends on the sensitivity of the organism to the Group 1 antibiotic If it is sensitive antagonism may result if it is resistant but not completely so synergistic action may be observed

Penicillin (Group 1) is most lethal against rapidly dividing organisms The bacteriostatic drugs of Group 2 exert their action by slowing multiplication of organisms thus creating the most adverse conditions for the bactericidal drugs Jawetz does not accept this facile explanation for antagonism between bactericidal and bacteriostatic agents but instead suggests that multiple interacting metabolic pathways essential for bacterial growth might be blocked simultaneously This hypothesis seems more in keeping with the experimental facts Jawetz has always advocated caution in the interpretation of these experimental facts and in attempting to predict the result of combined antibiotic action because the pattern of response varies with the experimental conditions employed

When should combinations of chemotherapeutic drugs be employed in practice? In the majority of rapidly responding acute infections highly sensitive organisms succumb even to antagonistic pairs of drugs The value of synergism arises under two circumstances (1) when the organism is not highly sensitive or is even on the verge of becoming resistant and (2) when the infection is a protracted one or so situated that it is relatively inaccessible to antibiotic action The best example of this is subacute bacterial endocarditis where an enterococcus of only moderate penicillin sensitivity is deeply embedded in fibrous tissue or cardiac vegetations The illness has smouldered for weeks or months before it has been detected clinically Synergistic action of penicillin and streptomycin under these conditions has been amply demonstrated when increased concentrations of either drug alone have proved ineffective

Tuberculosis is a chronic infection in which increasing drug resistance becomes evident when streptomycin is employed alone Tubercle bacilli lie embedded in a meshwork of fibrous tissue which prevents ready access of effective concentrations of the drug Bacterial resistance is prevented by giving a synergistic combination of any two of the three drugs streptomycin isoniazid and P A S Similarly in chronic brucellosis the intracellular situation of the organism makes it inaccessible to antibiotics Under these circumstances streptomycin may justifiably be combined with tetracycline

SYNERGISM AND ANTAGONISM

The development of resistance to one substance does not necessarily imply resistance to another Indeed the number and complexity of the metabolic pathways in bacterial nutrition would make it highly unlikely for several different and unrelated chemicals to behave similarly It was therefore inevitable that combinations of drugs should be employed in an effort to increase chemotherapeutic efficiency and to prevent the emergence of resistant organisms It was soon evident that not only could such combinations prove valuable but that they could also be mutually antagonistic These differing modes of action of combinations of drugs have been termed *Synergism* and *Antagonism*

A synergistic effect is defined as that in which the activity of two drugs in combination is *greater* than that obtained by doubling the concentration of either alone It implies a more profound effect than a simple additive one in which the antibacterial activity of the combination is equivalent to the sum of the actions of each drug when used alone

Drugs are said to be *antagonistic* when the antibacterial activity of the combination is *less* than that obtained with the most effective agent alone It implies interference of the activity of the combination by one or other of the components

The permutations employed in an effort to identify effective chemotherapeutic combinations has led to confusion especially between laboratory and clinical results Under differing conditions the same combination may be antagonistic or synergistic The painstaking pioneer work of Jawetz in this field has led to certain generalisations valuable in clinical practice Antibiotics are divided into two groups

Group 1	*Group 2*
Penicillin	The tetracyclines
Streptomycin	Chloramophenicol
Bacitracin	Erythromycin
Polymyxin	Novobiocin
Neomycin	

Group 1 drugs are bactericidal They are often synergistic, occasionally indifferent but never antagonistic to each other

Group 2 drugs are bacteriostatic They are neither synergistic with nor antagonistic to each other but additive effects are commonly

tant variants emerge as the dominant cells of the population The time and number of generations necessary before these mutants gain control varies with the antibiotic used and there are two distinct patterns Within a short time and in only a few generations a high level of resistance for example to streptomycin may occur This is called single step or streptomycin pattern resistance it is usually permanent and irreversible

In the case of the sulphonamides penicillin the tetracyclines chloramphenicol novobiocin polymyxin and bacitracin resistance increases gradually in the course of many generations each of which is only very slightly more resistant than the preceding generation This continual stepwise or penicillin type resistance is often reversible when the influence of the drug is removed

These two patterns of resistance are explained on genetic grounds The genes carrying penicillin resistance are of uniformly low potency and succeeding generations become gradually and increasingly resistant The genes carrying streptomycin resistance are of low and high potency Depending upon the type of mutation there will be an earlier development of moderate or high resistance

The pattern of resistance depends upon the antibiotic rather than the organism (Table 6) The same bacteria develop either pattern depending on the antibiotic to which they are exposed

MECHANISM OF DRUG RESISTANCE

Since the mode of action of antibiotics is unknown the mechanism of resistance is hypothetical Popular current theories are those of mutation and of adaptation of the organism to its altered environment

Antibacterial drugs alter fundamental physiological processes essential to efficient reproduction and continuity of the bacterial species This attack may be met defensively by a series of physiological modifications designed to ensure bacterial survival The resistance may occur rapidly in one step or in the course of several generations It may continue when the influence of the interfering antibiotic is removed, or it may only be temporary

The introduction of other agents can modify this sequence and this is the physiological basis of combined chemotherapy

The means by which the resistant variant ensures its survival may be

1 By development of an alternative metabolic pathway which by passes the one inhibited by the antibiotic
2 By producing a substance which is destructive to the antibiotic e g penicillinase produced by naturally occurring penicillin resistant staphylococci
3 By metabolic adaptation it may use the antibiotic instead of the normal metabolite This may proceed to complete dependence on the drug Streptomycin dependent organisms have been observed frequently
4 By producing an excess of substrate with which the drug competes for enzymes The best understood example is the increased formation of para aminobenzoic acid by sulphonamide resistant strains
5 By decreasing surface permeability and so preventing the drug reaching vital intracellular mechanisms

The cycle by which resistance is perpetuated must also be considered Because of their simple structure intimate contact with the environment and short generation time bacteria are essentially plastic and readily adaptable to the changing *milieu* Bacterial variants including drug resistant ones may arise by this adaptation to a drug-containing environment

The alternative and more widely held theory invokes mutational variants In any drug sensitive colony of organisms there exist a very small number of resistant mutants with a different genetic constitution When the sensitive population is destroyed the resis

Prevention and treatment

The indiscriminate use of antibiotics is to be condemned but cannot be halted The only practical means of minimising the use of penicillin is to avoid prescribing it in a relatively ineffective form This applies particularly to throat tablets chewing gum and to penicillin creams which are potent sensitisers

Mild reactions respond to oral or intravenous antihistamine drugs or to subcutaneous adrenaline Severe reactions may demand the early use of intravenous hydrocortisone Handlers of streptomycin powder particularly nurses should be warned to use protective gloves or a barrier cream on their hands from the moment they open the package until they have discarded the used syringe Not only may the hands be involved but also the face or any other part which may be touched Contact can be avoided by withdrawing the exact dose into the syringe directly from a rubber-capped vial

LOCAL TOXICITY

This includes the pain of injections of polymyxin and bacitracin injury to the sciatic nerve due to poor injection technique and phlebitis following intravenous tetracycline Intrathecal penicillin has been said to cause meningeal irritation but this was due to impurities which are rarely present in current commercial penicillins The value of intrathecal penicillin when indicated outweighs the rare risk of local reactions Oral penicillin preparations may cause varying degrees of black tongue a transient reversible phenomenon This has also been observed following oral tetracycline and chloramphenicol but it is of little import compared with the severe mucosal lesions which may follow their use The change in bacterial flora of the gastro-intestinal tract allows the overgrowth of saprophytes normally held in check by a balanced flora The most significant is Candida (Monilia) albicans which can cause stomatitis enterocolitis with diarrhoea proctitis pruritus ani and vaginitis If the drug is stopped the flora eventually reverts to normal and the mucosal lesions usually subside Sometimes it may be necessary to introduce another organism to suppress monilial overgrowth This is the basis for the former use of yoghourt which contains a harmless lactobacillus Oral nystatin is now preferred

Still more sinister is the development of enterocolitis due to a pathogen commonly Staph aureus which is resistant to the oral antibiotic being used (p 168) The sudden onset of severe diarrhoea

CHAPTER 3

COMPLICATIONS OF CHFMOTHERAPY

HYPERSENSITIVITY REACTIONS

THE widespread and often indiscriminate use of antibiotics has provided a sufficiently universal sensitising dose to allow subsequent hypersensitivity reactions when patients again receive the antibiotic (Table 6) These reactions develop not only in the allergic subjects but also in patients who had hitherto been free of sensitivity reactions Penicillin in particular, is responsible for both immediate (anaphylactic) and delayed allergic reactions These are not only due to its wide pread usage but also possibly because penicillin is the product of a fungus and shares some of the antigenic properties of this group Human fungal infections may therefore provide the initial sensitisation for subsequent penicillin hypersensitivity reactions Conversely, penicillin especially in ointment form is liable to exacerbate fungus infections of the skin

Immediate reactions are the more dramatic for laryngeal stridor or bronchospasm a shock like state or even sudden death may follow within minutes of the administration of penicillin Fatal reactions may follow intramuscular intravenous or intrathecal administration but they are extremely rare

Delayed hypersensitivity develops insidiously in the ensuing days or weeks following the first course or second dose causing serum sickness or skin rashes which may be urticarial vesicular erythematous or exfoliative

The drug fever and rashes which may follow therapy with sulphonamides streptomycin polymyxin the tetracyclines novobiocin vancomycin isoniazid and P A S are not so common or troublesome Contact dermatitis of hands and face may occur especially in nurses who handle streptomycin powder Swelling of the eyelids is an early manifestation of streptomycin sensitivity

On rare occasions sulphonamide hypersensitivity has provoked haemolysis and thrombocytopenia and it has been incriminated as a cause of subsequent periarteritis nodosa

Agranulocytosis and aplastic anaemia may follow chloramphenicol therapy Their occurrence with repeated courses suggested a sensitivity reaction but the nitrobenzene radicle contained in chloramphenicol is a well recognised direct depressant of the bone marrow

profound dehydration shock and collapse resembles cholera and it is associated with a similarly high mortality

Prevention and treatment

The undesirable effects on the gastro-intestinal tract usually subside following withdrawal of the drug and the return to a more normal intestinal flora Persistent and unpleasant pruritus ani and vulvae may be relieved by local hydrocortisone ointment

If monilial overgrowth is significant the fungicidal action of oral nystatin may prove helpful It should be given in addition if pro longed tetracycline therapy is contemplated

Staphylococcal enterocolitis demands early and energetic treat ment *Diarrhoea in a patient receiving broad spectrum antibiotics* demands immediate microscopy of the stools for Gram positive cocci Stool culture should also be performed although treatment should not be delayed until antibiotic sensitivity results are available Death is due to overwhelming toxaemia and also due to the pro found dehydration it is thus imperative to commence intravenous infusion as soon as the condition is suspected on clinical grounds The offending antibiotic should of course be withdrawn but it may be substituted by another to which the staphylococcus is sensitive This is usually the antibiotic in least current use or one of the several newly introduced anti staphylococcal agents such as erythromycin novobiocin oleandomycin or vancomycin

SYSTEMIC TOXICITY

Nephrotoxicity

The sulphonamides are liable to precipitate as crystals in the urinary tract Under conditions of extreme heat and in the de hydrated patient this may proceed to oliguria and anuria In the debilitated elderly and bed ridden patient the crystalluria may be a contributory factor to renal calculus formation

Three antibiotics in clinical use are directly nephrotoxic—neomy cin polymyxin and bacitracin In the case of neomycin this damage is sufficiently severe to preclude its parenteral use and con fine it to harmless topical applications or since it is poorly absorbed from the intestinal tract to oral use Polymyxin and bacitracin also cause albuminuria haematuria and casts in the urine The kidney damage is milder and reversible and in serious infections with organisms resistant to other agents slight nephrotoxicity is out

TABLE 6 —TOXICITY

Chemotherapeutic agent	Hypersensitivity reactions			Toxicity		Pattern of bacterial resistance
	Rash	Fever	Other	Local	Systemic	
Sulphonamides	+	+	Anaphylactic ?Periarteritis nodosa Blood dyscrasias	Contact dermatitis	Crystalluria { haematuria, anuria Methaemoglobinaemia	Penicillin pattern*
Penicillin	+	+	Anaphylactic	Contact dermatitis		
Tetracycline	Rare	Rare		Black tongue Gastrointestinal moniliasis Staphylococcal enterocolitis	→Cholera like picture	
Chloramphenicol			Marrow depression	As for tetracycline	Marrow depression	
Erythromycin and oleandomycin				Rarely vomiting and diarrhoea		
Streptomycin	+	+	Eosinophilia		Vertigo	Streptomycin pattern†
Dihydrostreptomycin	+	+	Eosinophilia		Deafness	
Neomycin				Oral→loose stools	Parenteral→nephro toxicity and deafness	
Polymyxin	+	+		Injection site pain	Transient paraesthesia ataxia nephrotoxicity	Penicillin pattern
Bacitracin				Injection site pain	Renal tubular necrosis	
Novobiocin	+	+	Eosinophilia		Yellow plasma	
Vancomycin	+			Phlebitis with i v route		
Isoniazid	+	+	Eosinophilia		Neuritis	Streptomycin pattern
P.A.S	+	+	?Cross sensitisation with chemically similar drugs	Anorexia nausea vomiting diarrhoea	Hypothyroidism Potassium deficiency Hypoprothrombinaemia	Penicillin pattern

therapy with P A S may cause hypothyroidism potassium deficiency and more rarely hypoprothrombinaemia

Prevention

Careful observation of the patient under treatment should unmask early evidence of toxicity If a patient receiving sulphonamides or chloramphenicol develops a sore throat or an unexplained recurrence of fever a leucocyte count should be done to exclude leucopenia The development of tinnitus may be a warning of streptomycin toxicity and audiometry is indicated The urine should be examined daily in patients treated with polymyxin and bacitracin

DRUG RESISTANCE

Undoubtedly the greatest disadvantage of chemotherapy when viewed as a world problem is the development of bacterial resistance (Table 6) Gradually increasing resistance of most pathogenic bacteria to the *frequently* used antibiotics makes the quest for newer agents more urgent and their appearance still more welcome In the control of infection succeeding antibiotics maintain control only as long as bacteria remain sensitive to them They are then superseded but may again be useful if organisms return towards their original sensitive status

Sulphonamide resistant gonococci provided an early warning of drug resistance Subsequently penicillin resistant organisms and streptomycin resistant tubercle bacilli have become commonplace Exemplifying the continuous warfare with each new antibiotic is Staph aureus Originally the vast majority were penicillin sensitive but now three quarters of *hospital* strains are penicillin resistant and nearly one half of these are resistant to the tetracyclines Erythromycin resistant organisms are also becoming increasingly common

Resistant variants in viral and rickettsial infections have not yet developed but this may be due to the relative youth of antiviral and anti rickettsial chemotherapy The mechanism of drug resistance is discussed on page 34

Cross resistance

Organisms resistant to certain antibiotics may be found naturally resistant to other antibiotics to which they have not been exposed This applies to the three tetracyclines if an organism is tetracycline resistant it is probably resistant to chlortetracycline and oxytetra

weighed by their distinct advantages as effective antibiotics Nevertheless the urine should be examined daily for albumin and casts, and blood urea determinations performed twice weekly

Neurotoxicity

Streptomycin damages the vestibular portion of the eighth cranial nerve leading to vertigo, which may be permanent In the early days of tuberculosis chemotherapy elderly people receiving large continuous doses were particularly affected Dihydrostreptomycin was introduced as an alternative, but it affected the auditory portion of the eighth cranial nerve, causing permanent deafness In choosing between these two drugs the possibility of vertigo must be balanced against possible deafness Vertigo can be compensated by eye reflexes and it is chiefly troublesome at night Deafness has no such compensation and this is a great argument against the use of dihydrostreptomycin Early objective evidence of eighth nerve involvement are high tone loss and high pitched tinnitus Patients even if elderly are unlikely to have this complication with a total dose of less than 25 g of streptomycin

Occasional reversible central nervous system signs including paraesthesiae ataxia diplopia and nystagmus have followed the use of polymyxin Peripheral neuritis is an infrequent accompaniment of isoniazid It is due to pyridoxine deficiency for the urinary excretion of this vitamin is greatly increased by isoniazid

Haematopoietic effects

Leucopenia agranulocytosis and aplastic anaemia have followed the use of sulphonamides and chloramphenicol Although these effects are exceedingly rare by comparison with the quantities prescribed they are sufficiently alarming to demand caution in the indications dose and duration of their administration

Others

Apart from these well recognised toxic effects on the kidneys nervous system and bone marrow there are also various systemic disorders which are less dangerous but worthy of early recognition They are peculiar to individual agents and they are infrequent Methaemoglobinaemia is no longer commonly seen in patients receiving sulphonamides During treatment with novobiocin a raised icteric index is occasionally noted It is thought to be due to a yellow plasma pigment metabolite of novobiocin Prolonged

resistant pneumonia only because they have failed to respond to oral penicillin or to intramuscular penicillin given for too short a time A good result may follow more intensive use of the same antibiotic

3 The causative organism is inaccessible to the antibiotic This *may be due to impermeable fibrous tissue any local abscess* should be drained and instilled with the appropriate antibiotic Alternatively organisms may be intracellular as in brucellosis where relapses are due to survival and eventual multiplication of the sheltered intracellular bacteria

4 Although the antibiotic may be effective against bacteria it will not neutralise toxin already present and toxaemia may persist Diphtheria is an example of this and it is imperative that antitoxin be used in such infections

5 Mixed infections may be difficult to control They demand careful assessment of the sensitivities of the bacteria concerned

6 The overwhelming nature of the infection the involvement of vital organs such as the adrenal cortex poor nutrition of the host accompanying chronic diseases such as hepatic cirrhosis alcoholism or nephritis coincident treatment with cortisone or corticotrophin These factors profoundly influence host resistance and may convert a mild infection to a fulminant one

cycline Erythromycin, carbomycin, spiramycin oleandomycin share resistance and streptomycin is linked with dihydrostreptomycin and neomycin The relationship seems to be chemical similarity

In this connection it might be noted that penicillin resistant organisms may become less resistant to penicillin after exposure to broad spectrum antibiotics or streptomycin This phenomenon is not understood but its practical implications are important

Prevention of resistance

This depends upon the following principles

1 High doses of the drug from the outset to minimise the development of bacterial resistance
2 Combined chemotherapy The best example of this is the addition of P A S or isoniazid to streptomycin in the control of tuberculous infection The incidence of streptomycin resistant strains of tubercle bacilli are markedly decreased The addition of oleandomycin to tetracycline or novobiocin to erythromycin may prevent the emergence of resistant staphylococci
3 Avoidance of the indiscriminate use of multiple antibiotics having an antagonistic action
4 New and chemically different antibiotics are more likely to be valuable than new but chemically similar analogues of their predecessors
5 Ringing the changes with various antibiotics may be commendable when judiciously employed The rest given to penicillin when the tetracyclines became popular has caused many penicillin resistant organisms to recover their sensitivity

CAUSES OF THERAPEUTIC FAILURE

When faced with an infection which does not appear to be responding to chemotherapy the possible causes include

1 The infection is due to antibiotic insensitive organisms or drug resistance is developing rapidly Antibiotic sensitivity tests of the isolated organisms are helpful before a change is made to the appropriate antibiotic or to combined chemotherapy which may halt the developing resistance
2 The antibiotic has been used for insufficient time Time and patience alone may correct this although many patients are referred to hospitals with the initial diagnosis of penicillin

PART 2

MICRO ORGANISMS CAUSING HUMAN DISEASE

CHAPTER 4

FUNGI

FUNGI are generally much larger than bacteria with a complex structure designed to permit both sexual and asexual means of reproduction Although grouped with fungi the actinomycetes occupy a half way house between fungi and true bacteria They are bacteria like in size and morphology but demonstrate branching which is a feature of fungi

Of the thousands of known fungi very few have been found pathogenic to man They can be subdivided into those causing superficial lesions and those producing deep seated infections Whereas the former are relatively innocuous the deep mycoses may be highly fatal or cause prolonged morbidity

SUPERFICIAL INFECTIONS

Fungal infections involving skin hair follicles and flexures are mild superficial localised and not fatal They have a world wide distribution but are prevalent in warm moist climates

DERMATOPHYTES

The dermatophytes consist of three genera of fungi—epidermophyton microsporum and trichophyton—which have a varying affinity for skin nails and hair (Table 7)

Epidermophyton Fungi of this genus have a predilection for skin and nails but the hair is not involved Epidermophyton floccosum causes ringworm of the groin and of the nails and also the common athlete s foot tinea pedis

Microsporum involves skin and hair but nails are unaffected Micro-

TABLE 7—ECTODERMAL TISSUES INVOLVED BY DERMATOPHYTES

Genus	Skin	Nails	Hair
Ep dermophyton	+	+	o
M crosporum	+	o	+
Trichophyton	+	+	+

from the lesions are placed on a glass slide a few drops of 20 per cent potassium hydroxide solution added a cover glass applied and the preparation heated slightly In preparations prepared direct from the submitted pathological specimen it is important to distinguish spores from fat globules and mycelium from fibrin strands

With the exception of Actinomyces israeli the fungi can be cultivated on routine media under aerobic conditions but their slow rate of growth demands that cultures should be maintained for two weeks and that they should be protected from drying Although they have no special nutritive requirements the addition of sugar is helpful peptone maltose agar is the basis of the traditional Sabouraud medium A skin test has been used for the diagnosis of Trichophyton gypseum infection (Table 24)

TREATMENT

Although there is no specific treatment for superficial fungal infections different fungicides have varying degrees of success

When accompanied by acute inflammation with oedema soothing applications containing boric acid or calamine should be applied as continuous wet dressings If there is little or no inflammatory reaction undecylenic or propionic acid ointments or Castellani s paint may be employed Hyperkeratosis is treated by keratolytic preparations such as salicylic and benzoic acid ointment massaged into the affected area nightly Dusting powders are invaluable in the prevention and treatment of uncomplicated superficial fungus infections of the skin

Various chemicals including gentian violet and sodium propionate have been recommended to control infections due to Candida albicans but it is more pertinent to determine the precipitating factor causing its overgrowth

Continued use of antibiotics is a major factor and they should be stopped The introduction of another organism in an effort to counterbalance C albicans is a basis for the use of yoghourt which contains a lactobacillus This was occasionally successful in balancing the mucosal flora and suppressing spread of monilia but the introduction of a fungicide nystatin has proved more effective in the control of monilial overgrowth Nystatin is given by mouth in doses of 1 mega unit daily in divided doses for intestinal moniliasis topically as an ointment or in the form of vaginal pessaries for monilial vaginitis

Fungus infections of the skin may provoke hypersensitivity

sporum audouini only occurs in man causing ringworm of the scalp The hairs are characteristically broken off a short distance from the surface of the scalp, leaving hair stubs surrounded by spores *Trichophyton* infections involve skin nails or hair Trichophyton gypseum causes the common tinea pedis or athlete s foot T tonsurans causes a scalp ringworm, T schoenleini is the cause of favus in the Mediterranean region, T rosaceum is responsible for a disfiguring ringworm of the beard

NOCARDIA MINUTISSIMUS

Nocardia minutissimus causes erythrasma This is a superficial mycosis affecting principally the groins but the axillae and inter gluteal clefts may also be involved It commences as a scaly macule which spreads slowly to form yellow or brown scaly patches with reddened edges

CANDIDA ALBICANS

Candida (Monilia) albicans has been recognised for over 100 years, but lesions due to it have become increasingly prominent since the introduction of the broad spectrum antibiotics It is an oval budding yeast like fungus which is present as a constituent of the normal flora of the mucous membranes When this flora is upset by intercurrent infections debilitating disease or over zealous use of antibiotics it may become the dominant growth and provoke lesions of the mucosa When involving the buccal mucosa it is commonly referred to as *thrush* but it may also cause red excoriated lesions of the skin flexures troublesome vulvo vaginitis and proctitis or even invade the lungs and large areas of the intestinal tract

MALASSEZIA FURFUR

This fungus causes a superficial skin lesion *pityriasis versicolor* characterised by circumscribed brownish scaling patches on the trunk and shoulders but with very little accompanying inflammatory reaction The patches show golden brown fluorescence in Wood s light The causative fungus has not been cultivated but its appear ance in scrapings is distinctive

DIAGNOSIS

The diagnosis is largely clinical based on the characteristic lesions and in particular their location Demonstration of mycelial elements and spores may be made by direct microscopy Scrapings

ASPERGILLUS FUMIGATUS

The bluish mould often present on stale damp bread belongs to the aspergillus group Aspergillus fumigatus is the pathogen most commonly associated with human infections It has long been recognised as a secondary invader of chronic suppurative lesions of the bronchi lungs pleura sinuses and ears It has been observed in chronic tuberculous cavities in gangrenous lung and also in foetid empyemas Despite the decline in incidence of these severe pleuro-pulmonary infections or perhaps because of specific anti bacterial chemotherapy *aspergillosis* is now seen in a more pure form The fungus may provoke a variety of chronic granulomatous lesions of the lung The radiological picture suggests cavitation fibrosis or solid lesions which may be confused with that of a tuberculoma or a peripheral bronchial carcinoma It seems possible that some of these lesions may be secondary to the prolonged use of antibiotics in the control of bacterial infections because fungal infections are prone to become dominant under such circumstances Systemic aspergillosis has been observed following antibiotic therapy Although flimsy this evidence is sufficient to counsel caution in the prolonged use of antibiotics in the control of bronchitis and other chronic bronchopulmonary affections

Treatment Intravenous hydroxystilbamidine 0 15 g daily for 10 days is worthy of trial Surgery is indicated for chronic per sistant pulmonary infection or if a solid aspergilloma of the lung cannot be distinguished with certainty from a bronchial neoplasm

CRYPTOCOCCUS NEOFORMANS

The encapsulated yeast like fungus Cryptococcus neoformans or Torula histolytica which has a world wide distribution is responsible for *torulosis* a disseminated granulomatous infection Clinical presentations include isolated subcutaneous abscesses pulmonary lesions or subacute meningitis (page 160) It may be confused with tuberculous or sarcoid meningitis both of which may exhibit simultaneous pulmonary and meningeal involvement

The causative organism should be sought in sputum and in the spinal fluid by direct microscopy using india ink or nigrosin to outline the capsule and specific antiserum to detect capsule swelling Specimens should be cultured on Sabouraud s medium and observed for up to one month

Treatment Local lesions are treated by surgical drainage and

reactions with other fungus products The most important and widely used product is probably penicillin Caution should therefore be exercised when prescribing penicillin in the presence of skin fungus infections

SYSTEMIC FUNGAL INFECTIONS

There remains a heterogeneous collection of fungi which produce deep and spreading lesions and may even endanger life by involvement of vital organs

ACTINOMYCES ISRAELI

The actinomycetes have certain features in common with bacteria especially mycobacteria and with fungi Actinomyces israeli is a Gram positive filamentous organism which shows true branching Unlike some actinomycetes it is non motile and is not acid fast It is the only pathogenic fungus which prefers to grow anaerobically

Although it may be found in the normal flora of the oropharynx tonsils or in decayed teeth under certain ill understood circumstances which may include a symbiotic alliance with bacteria it flourishes and provokes the chronic granulomata which are typical of *actinomycosis*

The common sites of involvement are cervico facial pleuro pulmonary and caecal areas The characteristic lesion is a hard red painless granuloma which develops insidiously eventually becoming fluctuant and discharging The pus contains masses of branching mycelia which resemble sulphur granules The resulting sinus tracts whether they open to the surface or form internal fistulae are slow to heal If the organism is not found in the exudate it should be sought in biopsies of the sinus tract

Treatment In vitro tests show that there is great variation in the sensitivity of this organism to penicillin and this antibiotic should be administered in large doses for a prolonged course of treatment Ten to twenty million units daily may be necessary to ensure that an adequate amount penetrates the fibrotic lesions and this should be continued for at least four weeks If penicillin appears to be ineffective, combined therapy with sulphadiazine and tetracycline should be tried Surgical drainage with instillation of the antibiotic of choice should also be undertaken It is possible that a major influence of the antibiotics is against the bacteria which accompany the fungus so depriving it of a symbiotic alliance which determines the pathogenicity

practically confined in its distribution to the North American continent Blastomycin skin tests would suggest a higher incidence of inapparent infections than that observed clinically A primary skin ulcer, usually on an exposed surface signifies a site of entry but primary pulmonary blastomycosis is also encountered suggesting a respiratory portal of invasion Blood borne dissemination involves lungs liver bones adrenal cortex, brain and other organs causing a serious generalised granulomatosis with a grave prognosis The fungus is found in sputum and by biopsy of involved organs

Treatment There is no satisfactory treatment but stilbamidine and undecylenic acid are worthy of prolonged trial Stilbamidine is administered in daily doses of 0·15 g intravenously for two weeks with rest periods between courses The initial dose of undecylenic acid is 5 g daily and it should be increased to a maintenance dose of 20 g daily by mouth for several months

COCCIDIOIDES IMMITIS

Unlike the other yeast like fungi Coccidioides immitis never reproduces by budding but by spore formation within the tissues It causes *coccidioidomycosis* which is endemic in the dry dusty areas of the south western United States and particularly prevalent in the San Joaquin valley of California Direct infection from man to man does not occur

The epidemiological and clinical aspects of this disease are in many respects similar to tuberculosis Primary coccidioidomycosis follows inhalation of the infective spore It may be asymptomatic and only eventually recognised by a coccidioidin skin test (Table 24) similar to the Mantoux test and by calcified lesions in chest radiographs alternatively it may present as erythema nodosum or with respiratory tract symptoms Progressive post primary or secondary coccidioidomycosis may ensue in the following year and results in thin walled cystic pulmonary cavities or in visceral central nervous system skeletal and subcutaneous granulomatous lesions

In order to distinguish it from tuberculosis an intensive search for the causative organism in sputum pleural fluid gastric washings spinal fluid and in biopsy material is necessary Serologically precipitin and complement fixation tests using coccidioidin antigen are useful in diagnosis and prognosis A high antibody titre in the complement fixation test is ominous and heralds progressive dissemination of the infection

Treatment Primary coccidioidomycosis like primary tuberculosis

radiotherapy Some success has been claimed following the use of actidione for torula meningitis which was otherwise always fatal

HISTOPLASMA CAPSULATUM

Skin tests and serological surveys in the U S A suggest that inapparent infection with Histoplasma capsulatum is more wide spread than would otherwise be suspected from the incidence of overt *histoplasmosis* Suggestive of such subclinical infection are patients with miliary calcification in their chest radiographs in whom the tuberculin test is negative but a histoplasmin skin test is positive The highest incidence is in the state of Ohio It commences as a respiratory tract infection following inhalation of spores contained in dust Infrequently there is widespread dissemination of the fungus with lymphadenopathy hepato splenomegaly, and granulomata involving many organs

The oval yeast like budding cells of H capsulatum measure 2 to 4 microns They may be recovered from sputum blood or sternal marrow scrapings from superficial lesions or from biopsies of lymph nodes spleen or liver They may be found within the cells of the reticulo-endothelial system or within the phagocytic cells of the blood or marrow Culture on Sabouraud s medium should be maintained for at least one month Intraperitoneal inoculation of mice may also be helpful

A complement fixation test shows a rising titre of antibodies within a few weeks of infection A high initial titre suggests previous infection and some measure of immunity

The histoplasmin skin test is performed like the Mantoux reaction and interpreted in the same manner (Table 24)

Disseminated granulomata with no evidence of circulating antibody carry a grave prognosis for there is no specific treatment The primary pulmonary form has an excellent prognosis and is indeed often only diagnosed retrospectively by routine chest radiography

This infection is now being recognised in spheliologist who contract the infection from cave-dwelling bats

Treatment There is no specific therapy

BLASTOMYCES DERMATITIDIS

Blastomyces dermatitidis is a budding yeast like fungus 8 to 18 microns in diameter It causes a chronic suppurative granulomatous infection *blastomycosis* somewhat similar to histoplasmosis but

CHAPTER 5

PROTOZOA AND METAZOA

PROTOZOA

PROTOZOA are unicellular organisms constituting a heterogeneous group varying in size complexity of structure and mode of reproduction For instance the relatively simple Entamoeba moves by extrusion of pseudopodia whereas the trypanosomes move by means of flagella Trichomonas divides by binary fission whereas the plasmodium group for example have achieved alternate sexual and asexual reproduction

ENTAMOEBA HISTOLYTICA (Table 8)

Entamoeba histolytica is a granular colourless nucleated mass of cytoplasm about $30\,\mu$ in diameter In its passage down the intestine it shinks into a more resistant cyst containing four nuclei a vacuole of glycogen and black staining chromatoid bodies Since most of the active motile amoebae are destroyed by gastric juice these resistant cysts are the forms passed in faeces and are responsible for spread of the disease Cysts rise to the surface of a 33 per cent zinc sulphate solution and can be identified by iodine staining this technique provides an easy means of isolating cysts from the stools in chronic dysentery

Actively motile multiplying amoebae penetrate the submucosa of the caecum and colon forming small abscesses which proceed to flask shaped ulcers or they may be contained in granulation tissue to form tumour like masses (amoeboma) Fibrosis and stricture formation may follow Passage of amoebae along the portal vein results in amoebic hepatitis and/or amoebic abscess of the liver

Diagnosis of amoebiasis should be suspected in any patient with intractable lower intestine symptoms especially if he has resided in the tropics (diagnosis and treatment p 170)

TRYPANOSOMES (Table 8)

Trypanosomes are transmitted to man by the bites of infected tsetse flies causing trypanosomiasis This infection therefore occurs in endemic belts inhabited by the tsetse vector There are three common species of trypanosomes related to distinctive endemic belts—T gambiense (Belgian Congo Gold Coast Cameroons

is largely self limiting and confers protective immunity to the majority of affected individuals Localised residual pulmonary cavities may be resected There is no effective treatment for the disseminated form of the disease although prodigiosin is said to have halted dissemination in a few Negro patients who seem to be particularly vulnerable to the progressive disease

SPOROTRICHUM SCHENKII

The genus Sporotrichum is commonly saprophytic in the plant kingdom but man may become infected by the pricks of thorns causing *sporotrichosis* Thus infection is more commonly seen in farm labourers and horticulturists Sporotrichum schenkii produces a granulomatous subcutaneous nodule up to three months after inoculation of an exposed part of the body This nodule may ulcerate and discharge a little thin pus, the regional lymph nodes become enlarged and hard and secondary nodules may appear in the course of the draining lymphatics Rarely there is dissemination of the fungus leading to granulomata of bones and lungs

The organism or its spores may be found in the discharge or from biopsy material and it grows readily in Sabouraud s medium

Treatment There is no specific therapy, but the local lesions eventually heal and this may be helped by oral potassium iodide

LEISHMANIA (Table 8)

Leishmania donovani causes visceral kala azar and L tropica leads to a cutaneous Oriental sore The organism is carried by sandfly vectors

The visceral form may have an acute onset with a characteristic double temperature peak in twenty four hours and with drenching sweats A protracted illness follows with wasting marked splenomegaly leucopenia and anaemia

The cutaneous form commences as an itching papule at the site of a sandfly bite This becomes larger indurated secondarily infected and eventually ulcerates with a hard red edge Bacterial contamination commonly masks the presence of the protozoon so mucopus should be removed by cleansing before the parasites are sought in the serous exudate or in the wall of the ulcer

Diagnosis is established by recovery of the protozoon from the blood lymph nodes liver spleen sternal marrow or scrapings of the cutaneous ulcer Intracellular Leishman Donovan bodies are displayed by Leishman or Giemsa staining of the aspirated material or following culture in special media

There are also blood changes which are suggestive of kala azar There is a marked neutropenia with relative mononucleosis and raised serum globulins for which Napier s formol gel test is positive (One drop of commercial formalin mixed with 1 ml of the patient s serum at room temperature causes solidification similar to boiled white of egg within twenty minutes or so)

Treatment The pentavalent antimony compounds are effective in kala azar Freshly prepared sodium antimony gluconate (pentostam solustibosan) may be administered intravenously or intramuscularly Ten per cent solution should be given in intravenous doses of 300 mg daily for one week Ethylstibamine (neostibosan) may be used intravenously as a 5 per cent solution it is said to be more effective but also more toxic

An unrelated synthetic aromatic diamidine pentamidine isethionate is an alternative effective agent in kala azar It may be given intravenously or intramuscularly in doses of 3 mg /kg body weight daily to a total course of 3 g

The cutaneous form responds less satisfactorily to chemotherapy Surgical debridement and antibiotics to control secondary bacterial infection are recommended to minimise the degree of scarring which occurs with healing

Nigeria) T rhodesiense (Rhodesia Mozambique) and T cruzi (Brazil and other parts of South America)

Within three weeks of being infected with T gambiense or T rhodesiense febrile lymphadenopathy develops with recurrent erythemas and oedema This septicaemic phase is followed by central nervous system signs from which the name sleeping sickness is derived T cruzi infection is distinctive to the Americas (Brazilian trypanosomiasis or Chagas disease) It develops acutely in children or more insidiously in young adults A local indurated oedematous reaction at the site of the bite is followed by regional lymphadenitis, septicaemia and finally involvement of the central nervous system cardiovascular system liver and spleen

Diagnosis Trypanosomes are found in the blood cerebrospinal fluid or by lymph node puncture Lumbar puncture may lead to infective blood penetrating the spinal fluid and it is advisable to delay this procedure until twenty four hours after the first dose of the anti trypanosomal drug

Auto agglutination of red blood corpuscles or a decisive fall in the erythrocyte sedimentation rate following pentamidine or suramin are suggestive of the disease

Treatment Apart from general and symptomatic measures this should be directed towards a rapid elimination of trypanosomes from the blood and other tissues six monthly drug prophylaxis in endemic areas and an intensive programme for the control of tsetse flies

Specific chemotherapy with suramin (antrypol Bayer 205 germanin) or pentamidine is effective against the blood borne trypanosomes but if there is cerebral involvement it is essential to use tryparsamide or Mel B which penetrates the blood brain barrier Mel B a compound of melarsen oxide and dimercaprol containing trivalent arsenic, is more toxic than tryparsamide and should be reserved for advanced neurological cases due to tryparsamide resistant trypanosomes

Suramin is given in 1 g doses intravenously every other day during the first week and then weekly to a course of 10 g Pentamidine is administered intramuscularly in doses of 3 mg /kg daily for ten days It should not be given to patients with renal disease

For nervous system involvement tryparsamide is given intra venously in doses of 50 mg /kg weekly for eight weeks Mel B is given by mouth or intravenously in courses of 1 to 3 mg /kg for four days

Plasmodium vivax falciparum malariae ovale	*Malaria* Benign tertian Malignant Quartan Ovale tertian	Bite anopheles mosquito	Man	Periodic rigors fever Splenomegaly	Blood films Therapeutic response	Prophylactic proguanil pyrimethamine or chloroquine Therapeutic chloroquine mepacrine or *quinine*
Toxoplasma gondii	*Toxoplasmosis* Congenital Acquired	Transplacental ?	Hares	Jaundice *Choroidoretinitis* Hydrocephalus Convulsions Febrile lymphadenopathy	Serum antibodies Dye test Skin test	Pyrimethamine Sulphadiazine
Trichomonas vaginalis	Trichomonas *vaginitis*	Venereal	Consort	Yellow green frothy vaginal discharge	*Flagellated organism* in vaginal discharge	Intravaginal stovarsol Treat infected consort
Giardia lamblia	Giardiasis	Faecal	—	Watery diarrhoea	Direct smear of faeces for organism	Mepacrine
Balantidium coli	Balantidiosis	Faecal	Pig	Chronic dysentery	Direct smear of faeces for organism	Oral stovarsol

TABLE 8 —PROTOZOAL INFECTIONS

Organism	Disease	Trans mission	Animal reservoir	Clinical features	Diagnostic methods	Treatment
Entamoeba *histolytica*	Amoebiasis	Faecal	Man	Chronic dysentery Amoeboma Liver abscess	1 Sigmoidoscopy→ *biopsy* 2 Hot stools 3 Hepatic aspiration 4 Response to emetine	*Colitis* Tetracycline + amoebicide *Hepatitis* Chloroquine ±aspiration
Trypanosoma gambiense rhodesiense	African trypanosomiasis (sleeping sickness)	Bite tsetse fly	Man cattle antelope	Febrile lymphadenopathy Meningoencephalitis	Trypanosomes in blood C S F lymph nodes	1 Fly control—D D T 2 *Suramin or* pentamidine 3 C N S involvement —tryparsamide or Mel B
cruzi	Brazilian trypanosomiasis (Chagas disease)	Bite flying bug	Opossum armadillo cat dog rodents	Oedema eyelids Lymphadenopathy Hepatosplenomegaly Myocarditis		
Leishmania donovani	Kala azar	Bite sandfly	Man dog	Twice daily fever Hepatosplenomegaly Anaemia	1 Protozoon in blood lymph node spleen bone marrow 2 Napier formol ge test 3 *Therapeutic* response	1 Fly control—D D T 2 Sodium antimony gluconate ethyl stibamine or pentamidine
tropica	Oriental sore			Papule→ulcer	Protozoon in ulcer scrapings	1 Control secondary bacterial infection 2 Surgical debridement

parasites are sparse and should be stained in dilute Giemsa solution Using Leishman s stain thin films may be used to confirm the species of parasite

Treatment

Prophylaxis Proguanil (paludrine) should be prescribed in 0 1 g doses daily for one week before and four weeks after leaving endemic areas For the indigenous population 0 4 g weekly is sufficient Proguanil is a relatively slow acting schizonticide It also has a true causal prophylactic effect against malignant falciparum infection inhibiting the pre and exo-erythrocytic stages of develop ment Pyrimethamine (25 mg) and chloroquine (0 3 g base) weekly are effective alternatives against parasites which develop proguanil resistance

Acute attack A rapidly acting schizonticide is essential Chloro quine has the advantages that it does not precipitate blackwater fever and it is effective against all forms of malaria It may be given by mouth intramuscularly or intravenously but its rapid intra muscular absorption makes the intravenous route unnecessary The oral dose is 1 g chloroquine base initially followed by 0 3 g daily for three days alternatively 0 2 g chloroquine base may be given intramuscularly every six hours for the first twenty four hours In children parenteral dosage should be calculated as 5 mg /kg daily

Quinine may be employed because of its rapid rate of action Its drawbacks are that it may precipitate blackwater fever it may lead to chronic latent falciparum infection intramuscular injections may cause abscess formation and the effects of cinchonism are unpleasant

Mepacrine hydrochloride is also sometimes used for the acute attack It is a schizonticide which acts on the early stages of the asexual cycle of all parasites and can effect radical cure of falciparum infection It is given in doses of 0 3 g thrice daily for the first day twice daily on the second day then 0 1 g thrice daily for five days

Prevention of long term relapses due to parasites other than P falciparum primaquin diphosphate an 8 amino quinoline drug has been used in adult doses of 15 mg daily for two weeks It is effective in eradicating the exoerythrocytic tissue stages of the parasite Since it is relatively ineffective against the asexual blood stage chloroquine should also be given Primaquine should not be combined with mepacrine which augments the risk of vascular haemolysis due to primaquine

PLASMODIA (Table 8)

The malaria parasites Plasmodium vivax, P malariae and P falciparum are responsible for three distinct types of fever, respectively benign tertian quartan and malignant malaria The parasite undergoes a sexual stage of development in the anopheline mosquito By the bite of an infected female mosquito infection is transmitted to man who is an intermediate host for the asexual stage of development of the parasite in human red blood corpuscles and liver (Table 9)

TABLE 9—MALARIA

Form	Benign tertian	Quartan	Malignant
Parasite	P vivax	P malariae	P falciparum
Incubation period (days)	6-16	16-40	5 10
Asexual cycle in man (hours)	48	72	24 48
Erythrocyte stage trophozoite	Early ring form Eosinophilic Schuffner dots in large pale erythrocyte	Early band form Fine Ziemann dots in unaltered or small erythrocyte	Small signet ring Maurer dots in shrivelled erythrocyte
↓ Rupture	↓ In peripheral blood	↓ In peripheral blood	↓ In internal organs
Merozoites	16	8	6-20
↓	↓ Attach to reticulocytes	↓ Attach to mature erythrocytes	
Gametocyte	Oval or rounded 7 10 μ		Crescentic 9 14 μ

Diagnosis The protean manifestations of malaria provide a challenge to the diagnostic acumen of the clinician It can only be met by being alert to the possibility of malaria in any pyrexial patient who has lived in an endemic area in the preceding five years and by frequent repeated examinations of thick and thin films of blood for the parasites Thick films are particularly useful when

Stovarsal vaginal pessaries inserted nightly for four to six weeks including menstruation are effective but may be followed by relapses Intravaginal insufflation of tetracycline is also occasionally used to eliminate secondary bacterial contamination but the local spermicidal effect of tetracycline is undesirable

Oral aminitrazole 0 1 g thrice daily for ten days to both male and female partners simultaneously has been claimed by some to be an effective means of eliminating the vicious reinfection cycle between consorts

GIARDIA LAMBLIA (Table 8)

This organism occurs in free flagellated and cystic forms It may be found in profusion in watery stools although it is not certain whether it is the cause or accompaniment of the diarrhoea Neverthe less mepacrine in doses of 0 3 g daily for six days effectively controls the diarrhoea with disappearance of the protozoon from the stools

BALANTIDIUM COLI (Table 8)

Both trophozoite and cystic forms occur The pig is a common reservoir host It may cause an uncommon chronic tropical dysen tery resembling amoebic dysentery The diagnosis is confirmed by finding trophozoites in the loose stools during an attack or cysts in asymptomatic carriers There is no specific treatment although oral stovarsol has been recommended

METAZOA

The helminths which infest man are classified into trematodes (flukes) cestodes (tapeworms) and nematodes (roundworms) (Table 20)

TREMATODES

The most important flukes are those which cause schistosomiasis (bilharziasis) The three main species encountered in man are *S haematobium* *S mansoni* and *S japonicum* Other flukes include *Paragonimus westermani* (pulmonary fluke) *Fasciola hepatica* and *Clonorchis sinensis* (liver flukes) and *Fasciolopsis buski* (intestinal fluke)

Flukes usually have leaf shaped unsegmented bodies and possess suckers and an alimentary canal The fertilised ova are excreted in the faeces and urine or expectorated in the sputum of the mammalian host They hatch in water to form ciliated embryos which invade

TOXOPLASMA (Table 8)

Toxoplasma gondii is an intracellular parasite about 4 to 7 μ long, with a distinct nuclear chromatin but no flagellae It has been identified in numerous animal reservoirs in different parts of the world It causes toxoplasmosis which may be congenital or acquired Congenital necrotising encephalomyelitis of varying severity is associated with hydrocephalus microcephaly and choroido retinitis and it may be followed by cerebral calcification Alternatively toxoplasmosis may present with neonatal jaundice and hepatosplenomegaly Acquired toxoplasmosis may simulate glandular fever and any patient with febrile lymphadenopathy and a negative Paul Bunnell test is suspect Previous inapparent infection has been revealed by serological surveys in otherwise asymptomatic adults

Diagnosis is confirmed by the demonstration of a rising titre of serum complement fixing or neutralising antibodies by cytoplasm modifying dye tests or by skin testing (Table 24)

Treatment The toxoplasma organism utilises the *p*-aminobenzoic acid folic acid metabolic chain for its nutrition Both the sulphonamides and pyrimethamine antagonise this chain sulphonamides by competing with PABA and pyrimethamine by interfering with the conversion of folic to folinic acid Since they block different parts of the metabolic pathway, the effect of the combination should be greater than either drug alone This is the rationale of the treatment of toxoplasmosis with pyrimethamine 75 mg daily and a sulphonamide such as sulphadiazine 1 g daily for ten days Supplements of folinic acid may reduce the toxicity of pyrimethamine to the host without affecting its action on the parasite

TRICHOMONAS (Table 8)

Trichomonas vaginalis is a motile flagellated protozoon often found in profusion in malodorous yellow or green frothy vaginal discharges In trichomonas vaginitis the vagina has a typical strawberry appearance

Diagnosis is confirmed by examination of the discharge either by hanging drop suspension or simply on a slide carrying a drop of saline

Treatment It is a difficult infection to eradicate because of the constant danger of reinfection of the female from a focus of infection in the consort It is therefore important to examine the male partner should trichomonas vaginitis prove chronic or recurrent

The swallowed ova of *threadworms* hatch in the intestine and the cycle is completed by their transfer from anus to mouth by the hands

The larvae or microfilariae of the gravid female *filaria* are conveyed to man by the bites of infected intermediate insect hosts

The gravid female of *Dracunculus medinensis* discharges its larvae from the legs of the host into water where cyclops acts as an intermediate host The water flea is finally swallowed in water and reinfects man

The swallowed ova of *Ascaris* hatch in the intestine to larvae which penetrate the intestinal wall invade the blood reach the lungs and then pass directly from the trachea to the oesophagus and back to the intestine

The worms of *Trichuris trichiura* inhabit the caecum and large intestine The gravid female lays eggs which are passed in the faeces and which develop on moist earth On ingestion they hatch in the duodenum and the emergent larvae migrate to the caecum and develop to the adult

The worms of *Strongyloides stercoralis* are found in the duodenum Eggs are laid which are hatched in the small intestine to rhabditoid larvae and these are passed in the faeces The larvae develop further on moist ground to filariform larvae which penetrate the skin Burrowing into a capillary the larvae reach the lungs and penetrating the alveoli crawl over the epiglottis and are swallowed so reaching the duodenum

The *diagnosis* and *treatment* of helminth infections are discussed on page 176 and Table 20

appropriate snails for their further development through a cystic stage to a free living aquatic or cercarial form Depending upon the species of fluke the portal of entry to man is through skin or intestine

CESTODES

Tapeworms possess a head with suckers a neck and flattened segments There is no alimentary canal so they derive nourishment directly from the contents of the small intestine *Taenia saginata* is 20 feet long and possesses about 2 000 segments, *T solium* is 10 feet in length with about 1 000 segments, and *Diphyllobothrium latum* is 30 feet long and has about 3 000 segments The intermediate host varies with the tapeworm being cow pig and fish respectively, for T saginata T solium and Diphyllobothrium latum Man is the accidental intermediate host for *Echinococcus granulosus* because the adult worm normally parasitises dogs

Ova are ingested by the intermediate host through faecal contamination of food and water They develop into larval cysts which invade blood and muscle The intermediate host is then eaten by the main host (usually man) and the cysts develop into mature worms Occasionally there is more than one intermediate host In the case of Diphyllobothrium latum the embryo passes through the water flea (cyclops) and fish to man

NEMATODES

Roundworms have long cylindrical unsegmented bodies which are tapered at both ends They possess an intestinal tract and body cavity Their size varies enormously between Trichinella spiralis cysts (¼ mm) hookworm (10 mm) threadworm (0 5 inch) filaria (2 inches) Ascaris lumbricoides (6 to 10 inches) and the female Dracunculus worm (3 feet) The life cycle varies with the species

The adult worm of *Trichinella spiralis* is present in the intestine of the pig From this site embryos penetrate the intestinal wall pass in the blood to muscle where cysts are formed The cyst-containing pig muscle is eaten by man with the subsequent development of adult worms in the human intestine and of a cystic stage as in the pig in human muscle

Hookworm ova are excreted in faeces and if they find suitably warm moist conditions they develop into larvae which return to man by penetration of the skin They eventually reach the upper intestine where they complete their growth into adult hookworms by way of the blood lungs trachea and oesophagus

plaques on the limbs The name pinta is derived from the variegated hue of the lesions

Treatment

These diseases respond dramatically to penicillin given in doses similar to those employed for syphilis Substantially smaller doses have also been used with equally good results As in syphilis, reversal of positive serology lags behind the clinical cure

The individual patient can be cured of yaws or pinta by chemotherapy but this is insignificant compared with the eradication of the disease from the community This demands intensive mass treatment of at least 90 per cent of the infected population In anti yaws compaigns a single injection of 1 mega unit of a long acting penicillin is given to each person with clinical yaws and half this dose to each contact It is difficult of course to define these contacts who may or may not have latent infection or may be incubating the disease When yaws is prevalent in a community it is wiser to afford it the widest definition and attempt to treat the whole community If this should prove impracticable the alternative is a campaign of selective mass treatment of household contacts

BORRELIA

BORRELIA RECURRENTIS

Borrelia recurrentis which causes relapsing fever is 10 to 30 μ long and 3 μ wide with irregular spirals spaced by about 3 μ It is larger longer and with more loose irregular coils than treponema Unlike Trep pallidum Bor recurrentis takes the usual bacterial as well as blood stains and it may be cultivated in blood-enriched media

Relapsing fever occurs in Eastern Europe especially Russia and in the United States It is perpetuated by ticks who e animal host (shrew mouse armadillo opossum squirrel monkey) varies with the country

Following an incubation period of one week there is an abrupt onset of rigors fever and malaise sometimes with jaundice splenomegaly and rose-coloured spots on the trunk After a few days the temperature subsides but recurs with diminishing severity weekly for four to ten weeks The febrile stage is that of a widespread septicaemia the organisms are easily found in the peripheral blood but less frequently in the urine During the afebrile stage antibodies can be detected in the blood by a complement fixation test A

CHAPTER 6

SPIROCHAETES

THE various members of this large family have a common appearance of slender coiled spiral which are actively motile Some of them lead a saprophytic existence in the normal mouth others are pathogenic, causing various generalised acute infections The pathogens are classified into the groups *Treponema*, *Borrelia* and *Leptospira*

TREPONEMA

The three important organisms of this group are Trep pallidum (syphilis) Trep pertenue (yaws) and Trep carateum (pinta) They are morphologically indistinguishable slender spirals 5 to 20 μ in length and 0 2 μ in thickness The spirals are regularly spaced at about 1 μ intervals The treponemes unlike the saprophytic spirochaetes have never been cultivated on artificial media but they may be visualised under oil immersion with dark field illumination Human infection with any of the three species of treponema is accompanied by positive serological tests of both complement fixation (Wassermann) and flocculation (Kahn) types

SYPHILIS

Syphilis is predominantly a venereal and/or congenital infection and it is discussed elsewhere (p 209 and Table 23)

Yaws and pinta are neither venereal nor congenital although they are spread by direct human contact

YAWS

Yaws is characterised by ulcerating wart like granulomata of the limbs Their similarity to raspberries has afforded the alternative name *framboesia* Bone is also commonly involved but in contrast to syphilis cardiovascular visceral or neurological involvement is rare

PINTA

Pinta is endemic in South America It differs from yaws in that the lesion is a non ulcerating erythematous papule which is followed in the course of months by pigmented and still later hyperkeratotic

organs particularly liver kidneys and muscle producing a clinical picture of fever jaundice haemorrhages and uraemia or occasionally meningitis

Diagnosis

In the first week of illness leptospirae are found in the blood becoming less evident with the development of antibodies at the end of the first week when they may be isolated from urine

During the first week As soon as possible after the onset of the illness blood should be drawn for

(a) Thick dry smears stained by the Giemsa method for demonstration of leptospirae
(b) Dark field search for leptospirae Results by this method are only reliably interpreted by an expert
(c) Culture in Noguchi s medium
(d) Intraperitoneal inoculation of plasma into guinea pigs Infected animals develop fever and jaundice within a few days and the organisms are demonstrable in their tissues
(e) Acute phase agglutinating or complement fixing antibodies
(f) Leucocyte count This is considerably raised up to 30 000/cu mm with a polymorphonuclear preponderance and possible mild thrombocytopenia This polymorphonuclear leucocytosis is valuable in the differential diagnosis from severe viral hepatitis

After the first week From the tenth to the twentieth day leptospirae may be demonstrated in the urine by dark ground illumination guinea pig inoculation or cultural methods Guinea pig inoculation may be positive but the organisms obtained from urine are often not viable

Complement fixing and agglutinating antibodies are now present in high titre reaching a peak in the fourth week Complement fixing antibodies disappear rapidly after recovery so they are not as suitable as agglutinating antibodies in serological surveys of past infection Leptospiral agglutination tests are positive if titres are above 1 300 especially if a significant rise in titre is demonstrable

Aspiration liver biopsy has been used for diagnosis Although the histological picture is not distinctive for leptospirosis it is quite different from virus hepatitis and culture of a portion of the biopsy provides a high recovery rate of leptospirae

Spinal fluid Even in the absence of clinical evidence of meningitis the cerebrospinal fluid may reveal a pleocytosis mainly lymphocytic

positive Weil Felix reaction can also be demonstrated with the development of agglutinins for Proteus OXK but not for OX19

Treatment

Insect vectors in endemic areas are controlled by D D T Both penicillin and the tetracyclines are effectively spirochaeticidal but should be given as early as possible in the febrile septicaemic stage

BORRELIA VINCENTI

Borrelia vincenti is an actively motile spirochaete 5 to 10 μ long with a variable number of shallow irregular spirals Along with other harmless spirochaetes it inhabits the normal mouth and throat Under certain circumstances of lowered resistance Bor vincenti combines with cigar shaped Gram negative rods Fusiformis fusiformis to cause an ulcerative tonsillitis (Vincent s angina p 206) These organisms are demonstrated quite readily and in profusion when a throat swab is smeared on a glass slide and this preparation is stained with strong carbol fuchsin

Treatment is described on page 207

LEPTOSPIRA

This species is 4 to 20 μ long with closely wound fine spirals It may be grown in special media or on the chorio allantoic membrane of the chick embryo

Although there are twenty related stains of leptospirae human infection in Great Britain is chiefly associated with L icterohaemorrhagiae and L canicola which are morphologically indistinguishable even by electron microscopy Animal infection particularly in rodents is widespread and this provides a reservoir for human infection

WEIL S DISEASE (L. icterohaemorrhagiae)

Rats are the most important vectors of L icterohaemorrhagiae which is excreted in their urine and faeces and so transmitted by contaminated food and water to man The portal of entry in man is the gastro-intestinal tract or through abrasions of the skin The highest incidence is in adult males particularly agricultural workers sewer workers coal miners and ditch diggers Weil s disease is also an occupational disease of fish cutters and is recognised as such for compensation purposes

Following an initial septicaemia the organisms settle in various

organs particularly liver kidneys and muscle producing a clinical picture of fever jaundice haemorrhages and uraemia or occasionally meningitis

Diagnosis

In the first week of illness leptospirae are found in the blood becoming less evident with the development of antibodies at the end of the first week when they may be isolated from urine

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Aspiration liver biopsy has been used for diagnosis Although the histological picture is not distinctive for leptospirosis it is quite different from virus hepatitis and culture of a portion of the biopsy provides a high recovery rate of leptospirae

Spinal fluid Even in the absence of clinical evidence of meningitis the cerebrospinal fluid may reveal a pleocytosis mainly lymphocytic

and it may also appear xanthochromic There is usually a normal sugar level and normal or slightly elevated protein value

Treatment

Gloves and rubber boots should be provided when the occupational hazard demands such protection bathing in stagnant water should be avoided and adequate measures for rodent control must be maintained

Penicillin streptomycin the tetracyclines and chloramphenicol are all effective in experimental animal infections, but the results of chemotherapy of human infection are conflicting This is largely due to its variable severity and to the fact that it often remains unrecognised until hepatic renal or circulatory complications dominate the picture At this late stage chemotherapy is probably less important than a careful fluid and electrolyte balance high carbohydrate intake and a restricted or even protein free diet In severe cases with oliguria or anuria the régime should be similar to the one employed for acute renal tubular necrosis

If the disease is recognised at an early febrile stage intramuscular penicillin should be administered in doses of 10 to 20 million units daily An alternative drug for oral use is tetracycline 2 to 4 g daily in divided doses for five to seven days

CANICOLA FEVER (L. canicola)

Dogs are common hosts to L canicola Human infection is acquired by contact with infected dog urine so it is more frequent in veterinarians laboratory workers and other dog handlers

The clinical picture may be indistinguishable from Weil s disease but it is generally milder and more apt to involve females A common presentation of canicola fever is that of benign aseptic meningitis (p 160 and Table 18) *Diagnosis* and *treatment* are the same as for Weil s disease

CHAPTER 7

MYCOBACTERIA

THIS group of rod shaped bacteria do not stain readily but once stained they resist decolorisation by strong acids or by alcohol hence the term acid fast bacilli Amongst them are a large number of saprophytes including the smegma bacillus, the timothy and the butter bacilli any of which may on occasions be confused morphologically with the pathogens of the group The saprophytes tend to be less acid fast they grow more luxuriantly on simple media with more pigmented colonies The important human pathogenic mycobacteria are Myco tuberculosis and Myco leprae causing respectively tuberculosis and leprosy

MYCO TUBERCULOSIS

Tubercle bacilli are thin rods varying in length from 1 to 4 μ and about 0 4 μ wide They grow slowly on special media the most popular in Britain being Lowenstein Jensen egg media The different strains—human bovine and avian—vary in their virulence for animals The guinea pig is usually employed since it is readily susceptible to both human and bovine strains

The tubercle bacillus contains protein polysaccharide and wax fractions all of which have a complex interrelationship Both protein and lipopolysaccharide fractions are antigenic and specific circulating antibodies for them have been demonstrated In addition they are capable of eliciting cutaneous hypersensitivity in the previously sensitised individual The protein fraction of tuberculin is responsible for the commonly performed tuberculin skin test The mycolic acid content of the wax fraction is claimed to be responsible for the acid fastness and virulence of the organism

The development of the tuberculous lesion is undoubtedly dependent upon these biochemical components which are as yet ill understood in addition to such other factors as the infecting dose of organisms received and the resistance of the individual

The primary tuberculous lesion is an acute exudative type of inflammation with rapid spread to the regional lymph nodes This is exemplified by the Ghon focus which may involve the lung and hilar lymph nodes or similar lesions in the intestine or tonsil

Clinical manifestations also include dry pleurisy or pleural effusion erythema nodosum or phlyctenular conjunctivitis

Subsequent reinfection leads to a more chronic type of lesion in which tissue necrosis and caseation is limited by a fibrotic reaction and regional lymph node involvement is minimal This is often termed the adult type lesion reinfection may be exogenous or endogenous usually the former It is commonly manifested by various forms of respiratory tuberculosis (Table 15) including laryngo tracheobronchitis bronchopneumonia lobar pneumonia and empyema fibrocaseous pulmonary cavitation or tuberculomas and also by intestinal tuberculosis

Between these primary and adult forms of tuberculosis range a large group of infections due to post primary dissemination of tubercle bacilli by haematogenous or lymphatic routes and by direct spread This may cause a generalised miliary infection meningitis (Table 17) renal disease (Table 21) bone and joint involvement peritonitis and lymphadenitis

Diagnosis

Tuberculin skin tests (Table 24) do not provide evidence of active tuberculosis but indicate hypersensitivity due to previous or current infection A negative tuberculin skin reaction is valuable in excluding infection due to the tubercle bacillus It is performed by the intradermal injection of 0 1 ml old tuberculin (O T) or the pure protein derivative (P P D) of tuberculin in dilutions of 0 01 mg (1 10 000) O T or 0 00002 mg P P D respectively If negative the test should be repeated with increasing concentrations until the response to 1 0 mg O T or 0 005 mg P P D is known A positive reaction is shown in forty-eight to seventy two hours by an area of induration exceeding 5 mm in diameter which may be surrounded by an area of erythema In children the test may be performed by applying a patch or strip of gauze impregnated with dried tuber culin The development in twenty four to forty eight hours of a red papule is approximately equivalent to a positive intradermal test using 0 1 mg O T

Isolation of the causative organism is the most important single piece of evidence in favour of active tuberculous infection In the respiratory disease it should be looked for in sputum laryngeal swabs or if necessary in resting gastric juice and washings Depending on the type of lesion the tubercle bacillus may also be present in pleural fluid early morning urine cerebrospinal fluid

tissue biopsies and the discharge from sinuses Numerous specimens should be examined and because large inocula are required for cultivation the specimen submitted to the laboratory should be generous and representative

Ziehl Neelsen stains or fluorescent microscopy will demonstrate the presence of acid fast bacilli In specimens of sputum cerebro spinal fluid and pleural fluid these are unlikely to be organisms other than tubercle bacilli but in gastric juice and urine saprophytic acid fast organisms are common Confirmation of their identity by culture and guinea pig inoculation is therefore essential

Radiological investigations include chest radiographs which are indispensable to the diagnosis of pulmonary tuberculosis and similarly intravenous and retrograde pyelography barium series and bone radiographs are important in defining renal intestinal and joint lesions

Biochemical investigations for tuberculous meningitis (p 159)

Surgical investigations may include cystoscopy laryngoscopy bronchoscopy pleural or pulmonary biopsy thoracotomy and laparotomy

Prevention

This demands the early detection segregation and treatment of infectious patients an improved standard of hygiene and of living generally and finally the use of B C G vaccination in selected groups Vaccination is particularly directed towards the children of tuberculous parents and personnel (nurses medical students) who are especially exposed to infection

Treatment

There are three drugs of proved value streptomycin isoniazid and paraminosalicylic acid (P A S) Although any one alone may be temporarily effective drug resistant tubercle bacilli eventually emerge This is largely overcome by the simultaneous administra tion of any two of these drugs Streptomycin is administered every twenty four hours in doses of 1 g intramuscularly whilst isoniazid is given by mouth in daily doses of 200 to 300 mg (3 to 8 mg /kg daily) and P A S in oral doses of 12 to 20 g daily Any two combinations may be adopted there is no contra indication to the simultaneous use of all three but it is wise to hold one in reserve Although chemotherapy has been stressed as the most important single factor it should always be regarded as complementary to the

traditional principles of adequate mental and physical rest good nutrition and when necessary surgery Surgical intervention includes measures designed to rest the involved tissues or to drain cold abscesses or measures devised to eradicate the tuberculous focus

The duration of chemotherapy depends in part on these complementary measures of rest and surgical intervention and it is therefore impossible to generalise other than that it should be continued for at least twelve months If streptomycin neurotoxicity becomes evident one of the other anti tuberculous drugs should be substituted

Since isoniazid diffuses through the body fluids so well it is valuable in the treatment of tuberculosis of serous surfaces It will probably eliminate the necessity for irritating intrathecal streptomycin injections in the treatment of meningitis although intramuscular streptomycin should be continued with it Combined streptomycin and isoniazid should be maintained for six months after the cerebrospinal fluid glucose level has returned to normal This implies a total course of chemotherapy of at least one year

MYCOBACTERIUM LEPRAE

Sparsity of knowledge about this chronic granulomatous infection stems partly from the fact that Myco leprae has not been cultured nor transmitted to animals The only source of the causative acid fast bacilli is the tissues of man in which they are particularly numerous in lepromatous leprosy

There are two distinct forms of leprosy lepromatous and tuberculoid but there are also some cases which cannot be categorised in this way and remain of indeterminate (borderline) type and prognosis

Lepromatous leprosy is characterised by ill defined shiny erythematous macules involving the skin of the face ears limbs and trunk symmetrically and by granulomatous involvement of the mucosal surfaces of nose mouth and larynx The conjunctiva cornea and uveal tract are often involved and may lead to eventual blindness The granulomata consist of vacuolated macrophages stuffed with lepra bacilli and by some epithelioid cells lymphocytes and fibroblasts which promote ultimate fibrosis particularly of the large peripheral nerves The bacilli may spread to involve lymph nodes, spleen liver bone marrow and testes Lepromatous leprosy is also characterised by the appearance of painful crops of erythema nodosum

In *tuberculoid leprosy* a defensive host response modifies the

clinico-pathological picture Acid fast bacilli are scanty or absent whereas epithelioid cells and giant cells are abundant with marked mononuclear infiltration These tuberculoid foci produce a well demarcated maculo papular cutaneous eruption which is anaesthetic and anhidrotic because of involvement of nerve endings in the corium The intense cellular reaction leads to fibrosis which involves nerves causing polyneuritis and leads to contractures and trophic ulcers Necrosis and absorption of bone together with muscle pareses lead to mutilating deformities Ulceration of macules is followed by healing with scar tissue

Diagnosis

The causative organism can be demonstrated in scrapings of involved skin or nasal mucosa stained by the Ziehl Neelsen technique They are abundantly evident in lepromatous leprosy but sparse or absent in the tuberculoid form of the disease

The lepromin skin test (Table 24) consists of the intradermal injection of 0 1 ml of lepromatous tissue antigen rich in bacilli The test is considered positive when an area of induration develops two days later (Fernandez reaction) and when a small nodule develops insidiously at the injection site in the course of three to four weeks (Mitsuda reaction) Biopsy of this site reveals a granuloma with epithelioid cells giant cells and some central necrosis

The test is positive in tuberculoid but negative in lepromatous leprosy It is therefore positive in the form of the disease in which there is a good host response so it does provide some measure of the immune status of the patient The test has the disadvantage of false positive reactions in both healthy and tuberculous subjects It has no diagnostic value but is helpful in classification and prognosis of the disease

Serological tests have no diagnostic value although circulating antibodies to the polysaccharide fraction of tubercle bacilli are readily demonstrated They are present in patients with lepromatous rather than tuberculoid leprosy—i e in patients in whom the lepromin test is negative

Treatment

Patients are segregated in leprosaria where they undergo a prolonged course of treatment with the sulphone group of drugs—promizole diasone and sulphetrone Any of these or a combination is administered orally for several years in ten week courses inter

rupted by rest periods Local hydrocortisone and oral cortisone are helpful in controlling allergic reactions especially erythema nodosum drug sensitisation uveitis and painful neuritis (p 223)

Treatment of anaemia intercurrent infections and complications together with physiotherapy and surgery for deformities are also most important

CHAPTER 8

GRAM POSITIVE BACTERIA

DIPLOCOCCUS PNEUMONIAE

THE organisms are lancet shaped diplococci with a surrounding capsule This capsule is a polysaccharide the specific soluble substance which is chemically and immunologically distinct for each type of pneumococcus When specific antiserum is mixed with pneumococci of the same type this capsule swells (Quellung re action) thus is useful in the identification and typing of these organisms The capsule protects the organism from phagocytosis and so it is partially responsible for the virulence of pneumococci The body as distinct from the capsule of the pneumococcus con tains a type specific protein and a group specific carbohydrate

Although they are often normal inhabitants of the upper respiratory tract a lowering of the body s defence mechanisms may cause pneumococcal septicaemia pneumonia (p 141) meningitis (p 156) mastoiditis and sinusitis (p 201) Throughout the years of penicillin therapy the pneumococcus has remained steadfastly sensitive so pneumococcal peritonitis osteomyelitis arthritis and endocarditis are no longer serious clinical problems

Diagnosis

The diagnosis of pneumococcal infections should be established by isolation of the organism from sputum blood or spinal fluid before treatment is commenced It may be difficult or impossible to obtain this proof if the patient has received penicillin within the previous twenty four hours The Quellung capsule swelling reaction using specific antisera may provide confirmatory evidence of the presence and type of pneumococci

Treatment

Penicillin is the drug of choice because the response is rapid and there are no complications The sulphonamides are also effective but their use in pneumonia is occasionally followed by post pneumonic effusions The organism is also sensitive to most other agents the exceptions being polymyxin and possibly streptomycin to which there are marked differences in the susceptibility of various strains

STREPTOCOCCUS PYOGENES

These spherical cocci are arranged in chains They contain antigenic protein, nucleoprotein and carbohydrate the latter forming the basis for serological grouping Various streptococci elaborate enzymes—streptokinase streptodornase and hyaluronidase as well as erythrogenic toxin and haemolysins

On the basis of haemolysis of blood agar, pathogenic streptococci are classified into three broad forms

Haemolytic streptococci whose haemolysins cause zones of complete β haemolysis of blood agar Specific antisera precipitate the corresponding carbohydrate antigen and allow their classification into Groups A to O The commonly found human pathogens are Group A haemolytic streptococci

Streptococcus viridans whose partial α haemolysis produces a green zone around colonies in blood agar They are normal inhabitants of the upper respiratory tract

Enterococci possess the characteristic carbohydrate antigen which places them in Group D Their haemolysis is variable Str faecalis does not produce a haemolysin although some other members possess this property They are normal inhabitants of the human intestine

Str pyogenes may cause upper respiratory tract infections (p 137) scarlet fever (p 204) pneumonia (p 141) empyema (p 147) endo carditis (p 149) and infections of the skin The latter include carbuncles erysipelas cellulitis impetigo and lymphangitis If the strain associated with erythrogenic toxin contaminates surgical wounds surgical scarlet fever may be a sequel

The relationship of Group A β haemolytic streptococci to rheumatic fever nephritis and erythema nodosum is more indirect because a hypersensitivity reaction rather than true septicaemia prevails Any of these illnesses may occur within three weeks of a streptococcal sore throat It has been suggested that the kidney damage is the result of an antigen antibody reaction within the glomeruli

Diagnosis

The organism is isolated from the throat blood or pus, and evidence of recent infection may be obtained by estimation of the anti streptolysin O titre This is of particular value in the group of

hypersensitivity diseases in which the organism cannot be isolated from the blood but only from the throat A significant rise in the serum anti streptolysin O titre suggests that the throat organism is causally related to the illness rather than an incidental finding

Treatment

β haemolytic streptococci are sensitive to penicillin which is the drug of choice although they are equally sensitive to several other agents Str faecalis varies in its degree of sensitivity to penicillin and the drug of choice must depend on antibiotic sensitivity tests A combination of penicillin and streptomycin may prove synergistic in infections due to this organism

Although antibiotics are ineffective for rheumatic fever recurrences of the disease are peculiarly prone to follow further streptococcal throat infections The susceptible individual should be protected by prophylactic courses of sulphonamides or penicillin alternately during the winter months or whenever he contracts a cold Similar chemoprophylaxis should be adopted in closed communities, as in the Services to suppress the spread of β haemolytic streptococci when epidemics of upper respiratory tract infections are imminent

STAPHYLOCOCCI

There are two important species Staph aureus and Staph albus the names depending on the colour they produce on blood agar plates

STAPHYLOCOCCUS ALBUS

Staph albus is a common inhabitant of the normal skin and it is not usually regarded as pathogenic

STAPHYLOCOCCUS AUREUS

Staph aureus may be found in the normal upper respiratory tract and carriers are frequently responsible for spread in confined communities such as hospitals The organism frequently causes human infections its pathogenicity being largely determined by its ability to produce the following substances

Thermolabile *exotoxin* and thermostable *enterotoxin* both of which cause marked inflammation and necrosis of tissues Enterotoxin causes one variety of food poisoning (p 166)

Coagulase which clots plasma in the presence of a reacting factor

in blood Coagulase positive Staph aureus is always pathogenic to man

Penicillinase, which destroys penicillin and contributes towards the development of penicillin resistant strains

Hyaluronidase and *fibrinolysin*, which facilitate the spread of organisms

The following infections are due to Staph aureus

Skin infections
Septicaemia
Osteomyelitis
Meningitis (p 156)
Pneumonia and empyema (p 141)

Skin Infections

A *furuncle* (boil) develops when inflammation of a hair follicle is accompanied by severe necrosis of its surrounding tissues This necrotic core is circumscribed by coagulated fibrin formed by the action of coagulase and by leucocytes and eventually by fibrous tissue All of these barriers militate against the successful penetration of antibiotics into the necrotic area

A *carbuncle* has the same pathogenesis but involves several follicles and extends more deeply into the subcutaneous tissue

Sycosis is also a staphylococcal folliculitis usually involving the mouths of follicles in different hairy regions particularly face scalp and nape of neck

Impetigo consists of intra-epidermal pustules, which coagulate to form yellow crusts (This infection may also be due to β haemolytic streptococci)

Pemphigus neonatorum, occurring soon after birth consists of vesicle and later bullous formation following umbilical sepsis

Septicaemia

Insignificant skin infections may lead to a bacteriaemia and this is followed by metastatic staphylococcal abscesses involving bone kidneys lungs, brain or other organs Alternatively, acute ulcerative endocarditis may be a sequel to this blood spread

Osteomyelitis

In the course of septicaemia Staph aureus may start a necrotic focus in the diaphysis of bone with formation of an abscess sequestra and new bone Depending on the balance between necrosis and

repair acute osteomyelitis may become a chronic focus which is punctuated by recurrent subacute exacerbations

Diagnosis

Culture of the organism from any of these involved tissues by inoculating blood agar plates with blood sputum spinal fluid or pus Its pathogenicity is assessed by the coagulase test and its ability to liquefy gelatin haemolyse blood or ferment mannitol may also be noted Antibiotic sensitivity should be determined as a guide to the best management Bacteriophage typing may be useful in epidemiological surveys

Treatment

Staphylococci continue to be the most difficult pyogenic cocci to control with antibiotics partly because of the selective propagation of antibiotic insensitive strains and partly because of the increased prevalence of acquired resistance About three quarters of hospital strains of staphylococci are resistant to penicillin These include both the strains found in penicillin treated suppurative lesions and also those carried in the nasopharyngeal flora and skin of hospital personnel and patients not receiving penicillin Penicillin resistant staphylococci are less frequent in out patients or in the general population varying from 20 to 50 per cent depending on previous penicillin treatment or previous hospitalisation Tetracycline resistant staphylococci are about one half as frequent as penicillin resistant ones Resistant variants are almost always hospital strains because the wide uses of antibiotics in such institutions have encouraged the development of drug resistant organisms It is fortunate that these strains are so far uncommonly encountered in the community away from hospitals

Faced with a staphylococcal infection in vitro sensitivity tests should be performed so that the most potent antibiotic may be chosen Until these results are available the clinician must choose the agent which is most likely to be successful If the infection has been contracted away from a hospital penicillin will probably and tetracycline will almost certainly be effective On the other hand serious infections contracted whilst in hospital should be treated at the outset with an antibiotic which is *in least current use in that particular hospital* This will ensure early control of the infection and may prevent an outbreak of ward cross infection Until recently erythromycin has been commonly kept in reserve for this

purpose and chloramphenicol was also returning to popularity despite its occasional haematopoietic toxicity Vancomycin novobiocin and oleandomycin now permit an even wider choice while streptogramin and its analogue E129 appear promising Combinations may delay resistance if they are not cross resistant members (Table 2, p 43) Erythromycin is the most potent of a family comprising oleandomycin spiramycin and carbomycin any of these may be combined with tetracycline novobiocin or vancomycin

CORYNEBACTERIA

These Gram positive rods include various saprophytic diphtheroids which inhabit the normal upper respiratory tract and also the pathogen *Corynebacterium diphtheriae* which elaborates a powerful exotoxin All three types of C diphtheriae—gravis mitis and intermedius—produce the same toxin which causes tissue necrosis locally and by absorption leads to nerve palsies myocarditis and involvement of liver kidneys and adrenal glands The rapid growth of this organism on the mucosa of nose tonsils pharynx larynx or in wounds leads to diphtheria (p 202)

Diagnosis

Nasopharyngeal or wound swabs are cultured on special media C diphtheriae appears as granular grey colonies on Loeffler s slants or greyish black colonies on tellurite agar media A blood agar plate should also be inoculated to exclude the presence of haemolytic streptococci which may produce the same appearances in the throat

Toxin producing organisms may be recognised by an in vitro toxin antitoxin precipitin test or by guinea pig inoculation, treatment should never await these results The Schick skin test is described in Table 24

Treatment

Treatment of diphtheria demands specific antitoxin and chemotherapeutic agents are of secondary importance (p 205)

CLOSTRIDIA

The Clostridia are anaerobic spore forming Gram positive rods widely distributed in nature and usually saprophytic to man On the basis of the lesions produced the important pathogens may be divided into two groups

Neurotoxic group in which the signs of disease are due to a

powerful neurotoxin Belonging to this group are *Clostridium botulinum* causing botulism and *Cl tetani* causing tetanus

Histotoxic group in which the organisms multiply in devitalised tissue especially muscle and destroy it by the direct and local effect of the clostridial toxins produced The organisms most frequently encountered in gas gangrene are *Cl perfringens* (*welchii*) *Cl novyi* (*oedematiens*) and *Cl septicum*

CL. BOTULINUM

Cl botulinum infection leads to botulism a fortunately rare variety of food poisoning (p 167)

CL. TETANI

Cl tetani infection causes tetanus Heat resistant spores of Cl tetani enter necrotic tissue which is possibly infected with pyococci and where the conditions are ripe for germination of this anaerobe After an incubation period varying from three days to three weeks the effects of its neurotoxin are noted The severity of tetanus depends on the period of incubation a short period being associated with a more fulminating course It is characterised by muscular spasms often commencing as trismus or lockjaw and involving other voluntary muscle groups to produce opisthotonos and generalised tonic convulsions Local tetanus in muscle groups adjacent to the site of infection is liable to occur in the partially immune Tetanus neonatorum may be the unfortunate sequel to umbilical sepsis

Diagnosis

The diagnosis is essentially clinical because treatment should not await the possible isolation of Cl tetani and proof of its toxigenicity

Treatment

200 000 units of tetanus antitoxin should be given intravenously to adults who are not hypersensitive to a test dose If necessary desensitisation should be carried out by gradually increasing doses

After administration of antitoxin it is safe to embark on surgical exploration of the wound to provide free drainage of purulent material excision of devitalised tissue and local insufflation of penicillin to control Cl tetani and other secondary bacterial con taminants Local injections of 20 000 units of antitoxin may also

be instilled around the wound Muscle relaxants are administered to control spasms

Following recovery the patient should be actively immunised with toxoid against any possible retained spores

Routine active immunisation of children and adults is best carried out by two doses of 0 5 ml alum precipitated toxoid at intervals of one month and followed by a booster dose in six to twelve months If the partially protected person subsequently needs more adequate protection his antitoxin level should be boosted by 0 5 ml fluid toxoid and preferably in addition 1,500 units of antitoxin

GAS GANGRENE ORGANISMS

Germinating spores especially Cl perfrigens Cl novyi and Cl septicum produce toxins locally in necrotic wounds, when secondary pyococcal contamination of devitalised muscle provides suitable conditions for them to flourish The foul odour of the discharge the local pain the oedema in crepitant gas producing tissues and the constitutional disturbance all contribute to a characteristic clinical picture Apart from anaerobic cellulitis and myositis following wounds gas gangrene may also complicate abortion causing uterine infection and septicaemia

Diagnosis

Since the diagnosis is essentially clinical little practical help can be gained from isolation of the clostridia and proof of their toxigenic qualities

Treatment

Treatment should certainly not await laboratory confirmation but is started immediately by the intravenous administration of 100 000 international units of polyvalent antitoxin preferably with a blood transfusion All infected tissues are radically excised and penicillin or tetracycline instilled locally Further intravenous antitoxin may be necessary twelve hours later An antibiotic cover of oral tetra cycline or intramuscular penicillin is necessary to control secondary infection and to aid the eradication of clostridia

BACILLUS ANTHRACIS

B anthracis is the only pathogen amongst a Group of Gram positive aerobic spore forming rods which includes *B subtilis*

The resistant spores of B anthracis are harboured in animal products such as hides wool and shaving brushes so anthrax is commoner in handlers of these infected products The spores enter an abrasion where the organisms proliferate and produce successively a papule vesicle and a malignant pustule containing a central black core of coagulated blood Although markedly indurated and associated with lymphangitis and enlarged local lymph nodes it is relatively painless Septicaemia may complicate this local lesion Inhalation of the spores may cause an acute bronchopneumonia and their ingestion has been known to cause severe ileocaecal ulceration

Diagnosis

The occupational history of exposure is noted and the appearance of the pustule may be characteristic

Swabs of the lesion show abundant encapsulated bacilli with Giemsa s stain This should be confirmed by culture and animal inoculation The anthrax bacillus may also be found in sputum blood or cerebrospinal fluid

Treatment

Treatment should be commenced as soon as swabs have been taken and without awaiting the result

The organism is sensitive to penicillin chloramphenicol tetra cycline and novobiocin The results of treatment with penicillin are excellent and it is unnecessary to resort to any of the other antibiotics

ERYSIPELOTHRIX RHUSIOPATHIAE

Erysipelothrix rhusiopathiae occurs in two forms a non motile non sporing Gram positive rod and a long and filamentous branching form It commonly infects pigs (swine erysipelas) and also occurs in sheep horses cattle fish and turkeys Man develops erysipeloid through skin abrasions by contact with these animals and their products Erysipeloid is more commonly an occupational disease of butchers cooks and fish handlers At the portal of entry a painful oedematous purple inflammatory reaction develops it has a distinct spreading margin and there is associated regional lym phadenitis Septicaemic spread with endocarditis has been known to follow local infection Penicillin and tetracycline are both effective in controlling the infection

CHAPTER 9

GRAM-NEGATIVE BACTERIA

NEISSERIA

N catarrhalis is found in the normal upper respiratory tract

The important pathogens of this group are *N meningitidis* and *N gonorrhoeae* In pathological material they occur intracellularly as kidney shaped diplococci, about 0 8 μ in diameter lying with their concave surfaces adjacent They are distinguished by their in vitro carbohydrate fermentations These organisms are strictly aerobic

N MENINGITIDIS

Man is the only natural host and the organism may remain as an apparently harmless commensal in the nasopharynx Under ill understood circumstances there may be a failure of the normal defence mechanisms which allows the organism to cause a local pharyngitis and to invade the blood stream A transient acute septicaemic phase may be followed by meningitis (p 154) purpuric skin eruptions or by adrenal failure It is now rare to see the picture of chronic meningococcal septicaemia in which organisms periodically invade the blood stream causing rigors fever prostration and petechiae on the trunk or erythema nodosum on the shins

The Waterhouse Fridericksen syndrome is an acute meningococcal septicaemia in which widespread haemorrhagic involvement of the adrenal glands accounts for profound circulatory collapse It is associated with a high mortality

Diagnosis

The delicate meningococcus is readily killed by drying chilling or sunlight so pathological specimens should be examined fresh and cultures promptly incubated

Direct microscopy Freshly made smears of the opalescent or purulent cerebrospinal fluid, stained with methylene blue show diplococci both in the leucocytes and lying free The organisms may appear to be scanty because meningococci autolyse rapidly

Culture of the organism should be performed from specimens of spinal fluid blood and from the aspirate of skin lesions The organism grows best in 5 to 10 per cent carbon dioxide at 37°C on

chocolate agar The medium should contain para aminobenzoic acid if there has been any possibility of the administration of sulphonamides before the specimen was taken Neisseria growing on solid culture media may be revealed by spraying the plate with 1 per cent tetramethylparaphenylenediamine hydrochloride which readily darkens them This is termed the oxidase test and applies equally to N gonorrhoeae

A precipitin test may be most useful when no organisms are visible in a smear of spinal fluid It is performed simply and rapidly by layering the fluid over anti meningococcal serum and noting the development of a precipitate at the interface

Treatment

Meningococci are highly sensitive to the sulphonamides and to penicillin The sulphonamides are preferable for the treatment of meningococcal meningitis because of their greater speed and certainty in crossing the blood brain barrier into the meninges (Table 17) In fulminant infections penicillin may be given intramuscularly in addition to a sulphonamide Adrenal cortical failure is corrected by glucose saline infusion intravenous hydrocortisone and other measures to maintain electrolytic control and a normal blood pressure

During epidemic periods spread of infection to contacts especially in closed communities such as the Services or in schools may be prevented by the prophlylactic oral administration of 2 g sulpha diazine daily

N GONORRHOEAE

N gonorrhoeae is a Gram negative diplococcus which is usually intracellular It differs from N meningitidis in its inability to ferment maltose It is the causal organism of gonorrhoea (p 213)

Diagnosis

Like N meningitidis it is a delicate organism so all pathological specimens should be examined fresh and cultures incubated as soon as possible (Table 23)

Direct microscopy Smears are prepared from secretions of the urethra if necessary after prostatic massage or from the cervix the conjunctiva or from aspirated joint fluid They are stained with methylene blue to demonstrate intracellular diplococci This appearance is not unique particularly in vaginal and conjunctival

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cyclines erythromycin bacitracin and polymyxin have all proved effective in the control of H influenzae infections Penicillin is completely ineffective and has in fact been used to enrich media for selective growth of H influenzae A combination of intramuscular streptomycin and oral sulphadiazine is suitable for respiratory tract infections but oral chloramphenicol with sulphadiazine is preferable for meningitis (p 157)

BRUCELLA

The causative organisms of brucellosis are Gram negative non motile aerobes comprising *Brucella melitensis* (goats) *Br abortus* (cattle) and *Br suis* (pig) The domestic animals associated with these three species provide a natural reservoir of infection and the disease is contracted by drinking infected milk, eating locally produced fresh cheeses or handling contaminated material It is therefore found in dairy and farm workers, veterinary surgeons and meat handlers

Brucellosis can be arbitrarily subdivided into acute subacute or chronic forms depending on the duration of disease Regardless of the severity of symptoms it is defined as acute if the illness is manifest for less than three months chronic if symptoms have occurred for over one year and subacute if intermediate in duration The chronicity which so readily develops in this disease and the relapses following treatment are largely due to the successful intracellular localisation of the organisms and parasitisation in the host s tissues

Following an incubation period of about two to three weeks there is a constitutional upset with anorexia weakness aching muscles and joints headache and an intermittent pyrexia ranging from 98 to 104 associated with severe sweating Almost half the patients have peripheral lymphadenopathy and splenomegaly hepatomegaly occurs less frequently This acute attack may subside spontaneously within three months or may be complicated by rare manifestations due to localisation of brucellae in various tissues These include central nervous system involvement spondylitis endocarditis pneumonia or hepatitis

Chronic brucellosis with repeated acute exacerbations may continue for several years Its indistinct clinical features may be confused with psychoneurosis and the diagnosis must be confirmed by laboratory methods

secretions, and the presence of the gonococcus should always be confirmed by culture

Culture of the organism from secretions should be performed as for N meningitidis The oxidase test is also positive

Treatment See page 213

HAEMOPHILUS

Several members inhabit the normal mucous membranes The three principal pathogens are *H pertussis* which causes whooping cough (p 139) *H ducreyi* which leads to chancroid (p 215) and *H influenzae* which causes infections of both respiratory tract (p 137) and meninges (p 157)

HAEMOPHILUS INFLUENZAE

H influenzae occurs in two forms with and without a capsule The capsule contains specific polysaccharides by means of which six specific types (*a* to *f*) of organisms may be distinguished by a simple capsule swelling reaction as for pneumococci (see p 77) It is doubtful whether the non-encapsulated organism frequently found in the normal nasopharyngeal tract is pathogenic Almost all meningeal infections are due to the encapsulated type *b* It gains access to the respiratory tract of susceptible infants causing a nasopharyngitis obstructive laryngitis or influenzal pneumonia this may progress by septicaemia to influenzal meningitis or pyarthrosis

The Koch Weeks bacillus has been held responsible for some outbreaks of epidemic conjunctivitis This bacillus is in fact indistinguishable from H influenzae

Diagnosis

H influenzae may be isolated from nasopharyngeal swabs blood pus or cerebrospinal fluid It can be identified within 30 minutes by adding type specific rabbit antiserum and observing capsular swelling The direct precipitin test is equally quick Spinal fluid is layered on this specific antiserum and the presence of capsular polysaccharide is shown by a precipitate at the interface This test is only applicable to a relatively clear fluid such as spinal fluid The organism may be cultured on special media

Treatment

The sulphonamides streptomycin chloramphenicol the tetra

Aspiration liver biopsy reveals miliary granulomata in a high percentage of patients with brucellosis Great care in interpretation is essential because similar miliary granulomata are also found in tuberculosis sarcoidosis and various fungal and viral infections The liver biopsy specimen like all other tissues should be routinely cultured

Treatment

The painstaking work of Spink and his group in Minneapolis on experimental infection in animals and tissue culture systems suggests that brucellae are rapidly cleared by leucocytes from the blood stream and are subsequently localised in the cells of the reticulo endothelial system Intracytoplasmic organisms develop a satisfactory *modus vivendi* finding it a suitable medium for multiplication and a protection against lethal phagocytosis Such successful intracellular parasitism may be likened to that displayed by viruses It is an important concept to an understanding of the relative failure of chemotherapy in both brucellosis and virus diseases Whereas extracellular brucella organisms are readily destroyed by antibiotics intracellular organisms remain resistant to all current forms of therapy

Acute brucellosis has been successfully treated by sulphonamides streptomycin the tetracyclines erythromycin and chloramphenicol but each has been followed by a high relapse rate This can be lowered by the simultaneous use of streptomycin and tetracycline and combined treatment is now a method of choice Tetracycline 0 5 g four times a day is combined with streptomycin 2 g daily intramuscularly for two weeks The patient becomes afebrile in three to seven days and the symptoms of arthralgia headache and malaise tend to disappear in eight days The common development of increased fever and symptoms within forty-eight hours of com mencing treatment represents a Herxheimer reaction which is both mild and transient

Relapses should be treated with further courses of chemotherapy if necessary changing the antibiotic or using a sulphonamide in conjunction with an antibiotic

Increased therapeutic success depends upon the development of chemotherapeutic agents which penetrate the host cell easily but without injury or by some method of dislodging organisms from their intracellular position The latter has been attempted but with little success by the use of cortisone and corticotrophin In mice

Diagnosis

Isolation of the organism is performed by culture of blood urine cerebrospinal fluid, bile, lymph node, liver or sternal marrow biopsy material in special media Br abortus alone of the three species needs 5 to 10 per cent CO_2 for growth Growth is slow and sub cultures should not be discarded as negative until six weeks after inoculation Blood culture is positive in about half of all cases, it is more likely to provide a positive result in the febrile ill patient and it is usually negative in chronic brucellosis

Serology Agglutinating antibodies develop during the second week of illness and persist for several years after recovery A potent antigen prepared from killed brucella organisms is titrated against serial dilutions of acute phase and convalescent phase sera A stationary agglutinin titre of about 1 100 suggests past infection but a significant rising titre in convalescent serum suggests active infection Skin tests with brucella antigen may provoke a rise in titre in the previously sensitised individual, so blood should be taken before performing the skin test

There is also a rapid bedside screening test (*Castaneda s method*) It is cruder than the multiple dilution tube method but it may provide an earlier answer The antigen consists of killed brucella organisms stained with methylene blue and titrated so that a positive reaction is obtained only when the patient s blood contains agglu tinins in a titre of 1 100 or higher One drop of this antigen is mixed on a glass slide with a drop of blood from the patient s finger Within 30 seconds a dark blue peripheral ring of agglutinated antigen appears distinct from a central red zone of erythrocytes

Brucellin skin test (Table 24) The antigen is a whole organism suspension termed brucellin It is inoculated either in a dose of 0 1 ml intracutaneously or in a thousand fold concentrated solution by the multiple punture technique using a Heaf gun Specific induration at two days indicates that at some time the patient has met brucella infection but it does not necessarily imply current infection The skin test may provoke a rise in titre of serum anti bodies especially if intracutaneous injections are repeated This response only occurs in the previously sensitised individual and strengthens the suspicion of previous infection The skin test does not provoke a significant antibody response in non sensitised persons It should always be interpreted in the light of clinical and serological findings A negative skin test does not exclude the diagnosis of brucellosis

does not necessarily imply a satisfactory response in any given infection because of other adverse contributory factors These include mechanical obstruction in the urinary or biliary tract peritoneal abscess formation gross pulmonary destruction with cavitation or the development of drug resistance It is therefore important not only to identify the causative organism but to assess its antibiotic sensitivity in order to plan the chemotherapeutic management in close conjunction with any indicated surgical intervention

Although simple urinary tract infections usually respond adequately to a sulphonamide recurrent or chronic infections demand careful investigation to ascertain their cause Otherwise continued chemotherapy can but lead to drug resistant pyuria Similarly the pyrexia and rigors of cholangitis cannot be controlled by antibiotics more than temporarily unless free drainage in the biliary tract is re-established

In the treatment of Esch coli septicaemia the choice of treatment lies between tetracycline a combination of sulphadiazine and streptomycin or polymyxin Chloramphenicol is also effective but the profusion of other effective agents makes it unnecessary

Pneumonia due to K pneumoniae may be recognised by its lack of response to penicillin it responds to large doses of streptomycin and sulphadiazine or to tetracycline (p 143)

PROTEUS INFECTIONS

The two species usually associated with human infections are *Proteus vulgaris* and *Pr morganii* They are actively motile pleomorphic organisms which split urea with the production of ammonia (The OX strains share specific polysaccharides with certain rickettsiae and this forms the basis for the Weil Felix test in typhus) Proteus organisms are normal intestinal inhabitants They are liable to provoke urinary tract infections which are troublesome because of their relative resistance to chemotherapy They may also be found as secondary invaders of chronic skin ulcers and of middle ear infections

In vitro sensitivity tests should precede therapy and the most effective antibiotic chosen Topically neomycin is probably the most useful Its toxicity precludes routine systemic use but it may be given intramuscularly as a life saving measure for fulminating Proteus septicaemia Urinary tract infections may be controlled by chloramphenicol or a combination of streptomycin and a sulphona

cortisone converts acute brucellosis into a fulminating and fatal infection but it is unable to alter the course of chronic brucellosis

THE ENTERIC BACTERIA

Bacteria of this large group are often normal inhabitants of the gastro intestinal tract of man and other animals Some lead a saprophytic existence there and only become pathogenic elsewhere as in the respiratory urinary or neurological systems Others are pathogenic in the gastro intestinal tract itself causing such diseases as typhoid and paratyphoid fevers Finally the prolonged use of oral antibiotics may lead to imbalance of the normal intestinal flora creating a new series of drug induced infections

THE COLIFORM GROUP

The coliform group are normal intestinal saprophytes which become pathogenic in other systems

Esch coli causes urinary tract infections septicaemia and meningitis peritonitis cholangitis and certain special types of this bacillus are implicated in epidemic diarrhoea of infants

The pathogenic role of *Aerobacter aerogenes* is confined to urinary tract infections in which it may accompany Esch coli in mixed infections

Klebsiella pneumoniae may rarely be isolated from the bowel or from the normal respiratory tract but under conditions of diminished resistance it may be responsible for severe pulmonary infections

Diagnosis

The clinical features of infections caused by these organisms vary with the site Laboratory confirmation of the diagnosis should be sought by

Isolation of the organism from urine blood spinal fluid peritoneal pus bile faeces or sputum by culture on blood agar or special media

Further biochemical differentiation by *fermentation reactions*

Direct capsule swelling test This is applicable to Klebsiella pneumoniae It may be performed on fresh specimens of sputum and may provide early confirmation in penicillin resistant pneumonia due to this organism

Treatment

The coliform organisms are sensitive to the sulphonamides tetracyclines streptomycin chloramphenicol and polymyxin This

SHIGELLA

These organisms have been differentiated into four groups by fermentation and antigenic studies The main types of each group are *Shigella dysenteriae* (*shiga* and *schmitz bacilli*) *Shig flexneri* *Shig boydii* and *Shig sonnei* (Sonne bacillus) Soon after contaminated food is eaten liberated toxins provoke an acute inflammation of the lower ileum and colon with abdominal pain diarrhoea and vomiting Bacillary dysentery of this type is restricted to the intestine and septicaemia is rare

Diagnosis and *treatment* are given on page 169

PASTEURELLA

Organisms of the Pasteurella group are non motile aerobic Gram negative rods They cause various severe infections in animals two of them *Pasteurella pestis* and *Past tularense* may be trans mitted to man causing respectively plague and tularaemia

PLAGUE (Pasteurella pestis)

Rats and other rodents provide a reservoir for Past pestis The clinical picture of the human infection depends on the route of transmission and portal of entry

Bubonic plague Infection is transmitted from rats to man by the bites of infected rodent fleas The lymph nodes draining the site of entry become enlarged to form buboes Extension of over whelming infections from this original site may lead to

Septicaemic plague with widespread involvement of all organs including lungs liver spleen and meninges

Primary pulmonary plague The portal of entry is the respiratory tract Inhalation of material from infected rodents or their carcases may give rise to a fulminant pneumonia from which highly infectious droplet particles may cause further spread

Diagnosis

Specific confirmation of the diagnosis rests upon isolation of the organism from sputum blood or the aspirate of buboes Smears are stained with methylene blue or by Gram s method and at the same time agar cultures and animal inoculation should also be undertaken Special stains may be used to demonstrate the bipolar configuration of the organism Serological antibodies may be detected during convalescence

mide, but the response is variable Proteus is moderately sensitive to novobiocin, and some strains respond to oral nitrofurantoin (p 195)

PSEUDOMONAS INFECTIONS

Ps pyocyanea (aeruginosa) may be found in normal faeces of skin, particularly when coliforms are suppressed It is pathogenic in mixed infections of the urinary tract or in chronic skin ulcers, especially when sensitive bacteria have been eliminated by chemo therapy Pseudomonas meningitis (p 158) secondary to chronic mastoiditis head injury or infected lumbar puncture is grave because of the relative resistance of the organism to chemotherapy It may also cause troublesome eye infections

Diagnosis is readily confirmed on culture by the presence of two water soluble pigments bluish pyocyanin and green fluorescein

Treatment

Pseudomonas is sensitive to polymyxin which should be adminis tered intrathecally for meningitis locally for chronic skin ulcers by subconjunctival injection for ophthalmic infections, and by instilla tion in sinuses or ears Results of treating chronic urinary tract infections are not striking because of underlying renal damage and obstructive lesions of the genito-urinary tract It should however be considered in conjunction with surgical measures when these are feasible

SALMONELLA

There are many important members of the salmonella family of Gram negative motile bacteria They may be subdivided into several groups on the basis of their heat stable somatic O antigens and within these groups individual types may be identified by their heat labile flagellar H antigens

Species peculiar to man are *Salm typhi* and *Salm paratyphi* causing respectively typhoid and paratyphoid A B and C fevers This group of infections is often designated enteric fever (p 172)

There is also a group of salmonellae usually found in animals but capable of human infection when ingested in contaminated food or water They may cause a septicaemia with or without preceding gastro enteritis

Diagnosis and *treatment* are given on page 173

PLEUROPNEUMONIA GROUP OF ORGANISMS

This ill defined group lies between bacteria and large viruses in morphology and growth characteristics Like bacteria they multiply on lifeless agar medium The colonies are minute and special techniques are necessary to visualise them Although they grow in cell free media they can also be propagated in the chick embryo Like viruses the organisms are filter passing and by means of gradocol membranes their size has been estimated to approximate to that of the larger viruses

They are known to cause epidemic pneumonia with pleural effusions in cattle and agalactia in sheep and goats but their role in human infection is undetermined The choice of generic name for the group is an unfortunate one when translated from veterinary to clinical medicine for they seem to play no pathogenic role in human pleural or pulmonary infections Various strains have been isolated from normal secretions of the respiratory and genito urinary tracts They have also been isolated from patients with prostatitis and with Reiter s disease in which non bacterial urethritis is associated with arthritis and conjunctivitis This is however insufficient evidence to recognise it as the infectious and causative agent of these diseases It has been suggested that male abacterial urethritis is contracted by intercourse with females harbouring pleuropneumonia organisms as part of their normal vaginal flora It is also possible that these organisms have a symbiotic role with other as yet unidentified agents in the production of disease

Sulphonamides and penicillin are ineffective but the tetracyclines and chloramphenicol inhibit these organisms in vitro

Treatment

Sulphadiazine, streptomycin, chloramphenicol and the tetracyclines are all effective in the control of plague It is preferable to use a bactericidal agent so streptomycin in doses of 2 g intramuscularly every day for one week is the drug of choice It should be combined with oral sulphadiazine The tetracyclines are kept in reserve as an alternative form of treatment

Prevention of the disease depends on rodent and flea control In the presence of severe exposure vaccination provides temporary protection

TULARAEMIA (Past tularense)

Rabbits and hares form the principal reservoir of infection from which Past tularense is occasionally transmitted to man by the bite of infected fleas or ticks by handling infected animals by inhaling their infected discharges or by ingesting contaminated food and water There are therefore several portals of entry producing distinctive clinical pictures which include cutaneous pulmonary oro pharyngeal abdominal meningeal and septicaemic tularaemia

Diagnosis

Laboratory confirmation should be sought by

Isolation of the organism from sputum blood buboe aspirate pleural or spinal fluid by culture on dextrose-cystine agar

Serological antibodies Agglutinating and complement fixing antibodies may be detected in convalescent phase sera

Skin test (Table 24)

Treatment

As with other Pasteurella infections Past tularense is sensitive to sulphadiazine streptomycin the tetracyclines and chloramphenicol The drug of choice is the bactericidal one streptomycin for the bacteriostatic drugs are liable to be followed by relapses As in the treatment of plague oral sulphadiazine should be given together with intramuscular streptomycin

VIBRIO CHOLERAE

Vibrio cholerae is a curved Gram negative rod actively motile because of a single terminal flagellum It possesses flagellar H and somatic O antigens It is the causal agent of cholera (p 174)

within the lining endothelium of blood vessels leading to vascular occlusion rupture and necrosis Similar involvement of the brain heart and other tissues may occur in the course of rickettsial septicaemia accounting for fever prostration and various localising signs

EPIDEMIC LOUSE BORNE TYPHUS (R prowazeki)

Although distribution is potentially world wide it tends to appear in epidemic form during wars when lack of hygiene in closed communities permits the ready spread of infected lice Following the louse bite an incubation period of up to three weeks precedes the onset of rigors fever malaise and generalised aches On the fourth day of the sickness pink spots appear on the trunk and spread to the limbs They may develop haemorrhagic centres become purple and finally deep brown The patient is shocked collapsed with a low blood pressure and there may be evidence of a myocarditis bronchitis and possibly encephalitis The features are those of widespread involvement of small vessels by multiplying rickettsiae Before the advent of broad spectrum antibiotics the fever lasted about two weeks and there was a mortality of about 20 per cent successful chemotherapy has considerably lowered these figures

MURINE FLEA BORNE TYPHUS (R mooseri)

Murine typhus is milder than epidemic typhus it has a shorter incubation period (six to fourteen days) and the vector is a flea rather than a louse Involvement of heart central nervous system and kidneys is less severe and the mortality rate even before antibiotics was less than 5 per cent

SCRUB TYPHUS (R tsutsugamushi)

The causative organism is transmitted by an infected mite The bite mark develops into an ulcer covered by a black scab and associated with regional lymphadenitis This characteristic eschar appears towards the end of the seven to fourteen day incubation period thereafter the clinical features resemble epidemic typhus The mortality rates in the days before specific chemotherapy were similar to those of epidemic typhus

ROCKY MOUNTAIN SPOTTED FEVER (R rickettsi)

Man is infected by the bite of rickettsia laden ticks After an incubation period of three to twelve days the clinical features resemble epidemic typhus but in contrast to typhus the rash

CHAPTER 10

RICKETTSIAE

INTERMEDIATE in character between bacteria and viruses are rickett siae which are transmitted to man by the bites of their natural hosts, the arthropods Rickettsiae are pleomorphic coccobacilli, about 300 to 600 millimicrons in diameter They divide like bacteria and when stained are readily visible under the ordinary microscope Also resembling bacteria are their enzyme systems which enable them to metabolise their own requirements and conversely makes them vulnerable to chemotherapeutic agents which interfere with this metabolism Like viruses they only grow in cell containing media They proliferate readily in numerous susceptible animals and in the yolk sac of the chick embryo

The generic name for this group commemorates Dr Howard Taylor Ricketts who died of typhus fever in Mexico City during the course of his investigations of this disease The diseases caused by the different members of the group are listed together with their characteristic Weil Felix agglutinations (Table 10) The general characteristics of rickettsial infections are fever varying degrees of constitutional upset and a rash Q fever is the sole exception in which there is no rash this originally led to diagnostic difficulties and hence the obscure title Q (for query) fever In the remainder the haemorrhagic skin lesions are caused by rickettsial mutiplication

TABLE 10—WEIL-FELIX AGGLUTINATION REACTIONS

Rickettsia	Disease	Proteus strain		
		OX 19	OX 2	OX K
R prowazeki	Epidemic louse borne typhus	+ + +	+	o
R mooseri	Murine flea borne typhus	+ + +	+	o
R tsutsugamushi	Scrub typhus	o	o	+ +
R rickettsi	Rocky Mountain spotted fever	+ +	+	o
R. conori	Mediterranean fever	+	+	o
R. pijperi	South African tick bite fever	+	+	+
R akari	Rickettsialpox	o	o	o
R burnetii	Q fever	o	o	o
R quintana	Trench fever		Not defined	

male guinea pigs or into the yolk sac of chick embryos R tsutsugamushi of scrub typhus can be isolated readily by intra peritoneal inoculation of the mouse *Rickettsiae stain blue with* Giemsa s or red with Macchiavello s stain

Weil Felix reaction The sera of patients with all rickettsial infections except Q fever and rickettsialpox agglutinate various strains of the Proteus bacillus This unexplained phenomenon was observed by Weil and Felix in 1915 and has become established as *an extremely useful test The Proteus group probably* share some antigenic component with the rickettsiae The agglutinins which develop in the course of infection affect variably different strains of Proteus vulgaris (Table 10)

Weil Felix agglutinins are detectable towards the end of the first week of the disease reach a peak at the end of the second week and the titre gradually falls off after one month The demonstration of a rising titre is more satisfactory proof of recent infection than a stationary level

False positive Weil Felix reactions are given by previous immuni sation with typhus vaccines by Proteus infections or by relapsing fever (p 67)

Specific serum antibodies Complement fixing antibodies appear in the second week of illness The titre increases to a maximum in the third week and declines slowly after two months Specific antigens are prepared by growing rickettsiae in the yolk sac of chick embryos and then purifying them

Specific serum antibodies are also demonstrated by their ability to agglutinate rickettsiae in vitro or to protect infected eggs or guinea pigs These methods are impracticable in routine laboratories which do not specialise in this work

Treatment

The control of epidemics consists in the delousing of populations by D D T the control of rats and mites and the clearing of their breeding places

The treatment of all these rickettsial infections has been revolu tionised by the introduction of chloramphenicol and the tetracyclines These antibiotics do not kill the rickettsiae but suppress their growth and spread in the body There is a dramatic response within one or two days of commencing treatment but since the antibiotics are only rickettsiostatic relapses are common The relapse responds

commences peripherally on the wrists, feet and forehead and proceeds centrally This variety is most prevalent in the western parts of the United States Somewhat similar tick bite rickettsial infections occur in the eastern United States (R akari) in South Africa (R pijperi) and in the Mediterranean area (R conori) The last three are also characterised by black eschars and the rash of rickettsialpox (R akari) resembles varicella

Q FEVER (R burneti or Coxiella burneti)

Although this is also a rickettsial infection, it bears little resemblance to those previously described It is not transmitted by an arthropod vector but by the ingestion and inhalation respectively of milk or air which is contaminated by infected tick faeces Although transmission is airborne person to person transference is extremely rare Further differences from the other rickettsial infections are the absence of a rash and a negative Weil Felix reaction

Although this infection was first described in Queensland the letter Q represents query rather than Queensland The term was introduced in 1937 by Derrick who had observed it for the preceding two years amongst employees in a Brisbane meat works in abattoir workers and in dairy farmers He showed that the blood and urine of infected patients contained an agent which could be transmitted to guinea pigs Burnet and Freeman using material supplied by Derrick demonstrated rickettsial bodies in the spleens of infected mice The causal organism R burneti was therefore named after its discoverer F M Burnet of Melbourne Because of its dissimilarities from other rickettsiae it has been reclassified in a separate genus as Coxiella (rather than Rickettsia) burneti This designation is in honour of H R Cox who in 1940 reported its existence in the United States

TRENCH FEVER (R quintana)

This louse borne infection occurred in Europe during the first World War It had the general characteristics of typhus it did not occur during nor has it appeared since the second World War Modern laboratory techniques have not been applied to characterise it distinctly

Diagnosis of rickettsial infections

Isolation of rickettsia Fresh whole blood from the febrile patient taken early in the disease may be inoculated intraperitoneally into

CHAPTER 11

VIRUSES

VIRUSES are filter passing particles of ultra microscopic size The largest are of the order of 300 millimicrons and the smallest recog nised 30 millimicrons They are only capable of growth and reproduction in the presence of living cells This precludes the use of the various agar media employed in bacterial culture Instead laboratory animals embryonated eggs or suitable tissue culture cells are required for their study in the laboratory These technical difficulties have confined our knowledge of the properties of viruses More recently the rapid growth of tissue culture techniques has augmented this meagre knowledge uncovered hitherto un recognised viruses causing infections and even unmasked orphan viruses for which no corresponding clinical infection has yet been adequately defined These have been provisionally designated ECHO (enteric cytopathogenic human orphan) viruses They are similar to the poliomyelitis and Coxsackie viruses and they may be causally related to one type of benign aseptic meningitis (Table 18) In no other field of infectious disease is the co operation of clinician and laboratory worker more essential in filling gaps in our knowledge of the relation of viruses to clinical disease

Because of our imperfect knowledge there is no satisfactory classification of viruses or their diseases Until such time as the causative virus is isolated from the infection with the same degree of routine facility as in bacterial infections a clinical classification is the most practical although perhaps not the most inquisitive for improving knowledge of the mode of spread and attack of the viruses

The following classification depends upon the affinity of viruses for certain systems and organs However many viruses are spread throughout the body during an initial viraemic stage This is unfortunately ignored in a classification which only takes into account a secondary or transient affinity for a certain organ Further more during its stage of general circulation the virus may produce clinical manifestations in several different systems simultaneously For the sake of clarity only the more important or obvious clinical presentations can be listed the alternatives are discussed under the individual diseases

to further treatment readily, suggesting that the relapse is not due to the development of resistance against the antibiotic

If the patient is moribund it may be necessary to administer the antibiotic intravenously in a drip transfusion of glucose saline until the patient is able to continue with oral therapy In the severely ill patient the cortisone group of drugs may be given in addition to the antibiotic as a rapid means of ameliorating the toxaemia

Successful chemotherapy has not completely obviated the need for active immunisation which effectively reduces the severity and mortality of typhus fever Effective vaccines are prepared from infected yolk sac membranes of chick embryos Two subcutaneous inoculations of 1 ml in the course of two weeks are followed by a booster dose during periods of undue exposure Either chloramphenicol or tetracycline may be used prophylactically in oral doses of 3 g once weekly it protects the patient from clinical disease, although rickettsiae are still evident in the blood

response or by demonstrating characteristic pathological changes in the patient s tissues

To improve this co-operation the clinician must know the laboratory worker s requirements in any given case he must know which are the most appropriate specimens the optimum stage of the disease for their collections and the value of paired acute phase and convalescent sera for demonstrating rising antibody titres

ISOLATION OF THE VIRUS

Isolation of the causative virus is often difficult time-consuming or even impossible Such work is rarely undertaken in routine hospital laboratories but only in specially-equipped virological units Until recently this entailed the upkeep of a variety of animals such as monkeys ferrets guinea pigs hamsters rabbits dogs and mice for propagation of different viruses This has become less cumbersome by the use of tissue culture and chick embryo techniques either of which is readily adaptable to any standard laboratory Animals are still useful vehicles for propagation of certain viruses—e g one-day old suckling mice are particularly helpful in the isolation of the Coxsackie and herpes simplex viruses

Cultivation in cultures of living tissue fragments is usually done in flasks or test tubes The tissue is embedded on the glass wall in plasma clot and bathed by special nutrient fluid The outgrowth of the fibroblasts and epithelial cells from the tissue may be observed under the low power of an ordinary microscope Certain viruses when inoculated into this system cause degeneration of these outgrowing young cells This is termed a *cytopathogenic effect* Specific antisera prevent virus growth and protect the growing cells from degeneration This inhibition of cytopathogenic effect is proving useful in typing strains of viruses and also in measuring the amount of serum antibodies which develop during convalescence

Certain viruses and rickettsiae grow in the fertile hen s egg The specimen is inoculated into the chorioallantois amniotic or allantoic cavities into the yolk sac or on occasions directly into the chick embryo The living chick embryo chosen for these procedures is usually between three and twelve days old

The specimen submitted to a laboratory equipped to perform the above techniques may consist of nasopharyngeal washings spinal fluid blood faeces saliva conjunctival scrapings vesicle or pustule fluid or portions of lung brain or spinal cord removed at autopsy The specimen should be taken at the height of the illness since

Rash producing
- Variola (smallpox)
- Varicella (chicken pox)
- Herpes zoster
- Herpes simplex
- Measles
- Rubella (German measles)

Respiratory tract
- Influenza
- Common cold
- Adenovirus infection
- Psittacosis

Neurotropic
- Poliomyelitis
- Rabies
- Lymphocytic choriomeningitis
- Arthropod borne encephalitis

Hepatitis
- Infective
- Serum

Ophthalmic
- Trachoma
- Inclusion conjunctivitis

Miscellaneous
- Mumps
- Infectious mononucleosis
- Yellow fever
- Lymphogranuloma venereum
- Sandfly fever
- Dengue
- Coxsackie virus infections

LABORATORY DIAGNOSIS (Table 11)

The diagnosis of some virus infections can be made at the bedside, others require close co-operation between the clinician and laboratory virologist Each may play an important role in the management of the patient and even the outcome of an epidemic The clinician from the history epidemiological data and clinical findings may narrow the differential diagnosis or indeed reach the correct diagnosis The laboratory worker may confirm the diagnosis by isolating the aetiological agent by showing a specific immunological

Disease	Incubation period (days)	Virus grown in	Virus recoverable from	Serological tests	Inclusion bodies in
Hepatitis (a) infective	15 40	Man ?Tissue culture ?Fertile egg	?Blood ?Faeces	—	—
(b) Serum	60-160	Man	?Blood only	—	—
Trachoma and inclusion conjunctivitis	4 12	Monkey	Conjunctiva	C F T using psittacosis —L G V antigens may be positive because of antigenic similarity	Scrapings from tarsal conjunctiva
Mumps	17 21	Fertile egg Monkey Tissue culture	Saliva Cerebrospinal fluid	C F T Haemagglutination inhibition test Tissue culture neutralisation	—
Infectious mononucleosis	5 10	—	—	Blood picture Paul Bunnell	—
Yellow fever	3 6	Mouse Monkey	Blood	Animal neutralisation	Liver
Lymphogranuloma venereum	3 21	Fertile egg Mouse	Bubo pus	C F T	Lymph node or granuloma
Sandfly fever	2-6	Mouse	Blood	Haemagglutination inhibition Animal neutralisation	—
Dengue	5-9	Mouse Tissue culture	Blood	C F T Haemagglutination inhibition Mouse neutralisation	—
Coxsackie infections	2 9	Suckling mouse Tissue culture	Nasopharynx Faeces Cerebrospinal fluid	C.F T Neutralisation in mice or tissue culture	—
Cold haemagglutinin pneumonia	16-25	—	—	Cold haemagglutination Streptococcus M G	—
Q fever	19	Fertile egg Mouse Guinea pig	Nasopharynx Blood	C.F T	—
Typhus	8 18	Guinea pig Fertile egg	Blood	Weil Felix C.F T Agglutination Animal neutralisation	—

TABLE 11 —LABORATORY DIAGNOSIS OF VIRUS AND RICKETTSIAL INFECTIONS

Disease	Incubation period (days)	Virus grown in	Virus recoverable from	Serological tests	Inclusion bodies in
Smallpox (variola)	12	Fertile egg	Vesicle Pustule Blood	C F T * using vesicle fluid	Vesicles
Chicken pox (*varicella*)	12 16	?Tissue culture	Vesicle fluid	?Tissue culture *neutralisation*	Vesicles
Herpes zoster	7 14	?Tissue culture	Vesicle fluid	?Tissue culture neutralisation	Vesicles
Herpes *simplex*	3	Fertile egg *Newborn mouse* Rabbit cornea	Vesicle *Saliva* Cerebrospinal fluid	C F T *Neutralisation in eggs or mice*	Vesicles
Measles	11 14	Monkey Tissue culture	Nasopharynx Blood	Tissue culture neutralisation	—
German measles (rubella)	16-18	Monkey	Blood Nasopharynx	—	—
Influenza	1 2	Fertile egg Mouse Ferret Tissue culture	Nasopharynx Lung	C F T Haemagglutination inhibition	—
Common cold	Up to 3	?	?	—	—
Adenovirus pharyngitis	1 3	Tissue culture	Nasopharynx	C F T Tissue culture neutralisation	—
Psittacosis	4 15	*Fertile egg* Mouse	*Nasopharynx* Blood Lung	*C F T*	*Lung* Spleen Lymph nodes
Poliomyelitis	4 35	Monkey Tissue culture	Faeces Nasopharynx Spinal cord	C F T Tissue culture neutralisation	—
Rabies	10 200	Mouse Rabbit Dog *Fertile egg* Tissue culture	Saliva Brain Spinal cord	Neutralising and complement fixing antibodies after *vaccination*	Negri bodies in *hippocampus*
Lymphocytic chorio-meningitis	1 3	Mouse Guinea pig	Blood Cerebrospinal fluid Brain	C F T Animal neutralisation	—
Encephalitis (St Louis Western and Eastern equine, louping ill)	4 21	Mouse Fertile egg	Blood Cerebrospinal fluid Brain Spinal cord	C F T Animal neutralisation	—

*C F T = *Complement fixation test.*

This experiment shows a two tube or fourfold increase which is significant Such tests have the advantage that they can be performed in any laboratory where Wassermann tests are undertaken without recourse to animal work.

The in vitro haemagglutination inhibition test

This test is easy to perform and may be used in the diagnosis of influenza mumps sandfly fever and dengue the viruses of which are capable of agglutinating red blood corpuscles The test depends upon the ability of the patient s serum (when it contains antibody) to inhibit haemagglutination by these viruses Doubling dilutions of serum are titrated against constant amounts of virus antigen and red blood corpuscles are added as indicator for the presence of free virus The highest dilution which inhibits agglutination is taken as end point There should be at least a fourfold increase in titre in the convalescent as compared with acute phase serum

Typical result (after Horsfall 1950)

Serum	1 10	1 20	1 40	1 80	1 160	1 320	Titre
Acute	o	+	+	+	+	+	1 10
Convalescent	o	o	o	o	+	+	1 80

o = haemagglutination inhibited
\+ = haemagglutination

The acute phase serum has prevented haemagglutination at 1 10 whereas the convalescent serum inhibited agglutination at 1 80 This indicates a significant increase in titre of antibody

Neutralisation tests

These tests compare the ability of acute phase and convalescent phase sera to neutralise the appropriate virus infection in a number of test animals or eggs or to prevent cytopathogenic effects in tissue culture Several groups of animals (or eggs or tissue culture tubes) are infected with the standard virus and each group is inoculated with varying dilutions of the patient s serum The survival rate in the varying groups is an index of the amount of antibody in the serum This method is employed only when absolutely necessary because of the cost and complexity of the experiment It is impractical for routine hospital use but remains an important research tool For the diagnosis of some viral diseases it is essential, because the simpler in vitro complement fixation test has not been developed

clearly isolation of the virus is more likely at this time than at the stage of convalescence Penicillin (500 units/ml) and streptomycin (1 mg/ml) are added to suppress bacterial growth in the specimen These antibiotics do not affect proliferation of viruses except those of the psittacosis lymphogranuloma group (When members of this group are suspected antibiotics and sulphonamides should not be added to the specimen) The specimen is then frozen in a thermos flask packed with carbon dioxide snow and transmitted to the laboratory without delay

SEROLOGICAL TESTS

Serological tests show an immunological response by the patient and are easier to perform quicker and provide a satisfactory answer in many virus infections They depend upon the demonstration of a significant (at least fourfold) rise in the titre of specific antibodies in convalescent phase as compared with acute phase, sera They suffer from the disadvantage that confirmation of the diagnosis may only be retrospective although high acute phase serum titres may be a helpful provisional guide Blood (10 ml) must be collected as early in the disease as possible and again two or three weeks later *It is spun in the centrifuge and the sera stored at* 4°C until used If the opportunity of securing acute phase serum has been missed, two serum specimens, separated by an interval of two weeks should still be taken These specimens may show a significant fall in titre of serum antibodies this is not such decisive information as a rise in titre, but it is nevertheless more significant than a persistently stationary level

Serological methods include the in vitro complement fixation test using virus antigen the in vitro haemagglutination inhibition test and neutralisation of infection in animals eggs or tissue culture

The in vitro complement fixation test

Potent virus antigen is titrated against serial dilutions of the patient s serum *the highest dilution of serum in which complement* is fixed is the end point A fourfold or greater increase in titre in the convalescent as compared with the acute phase serum constitutes a significant antibody response A typical result shows

Serum	1 10	1 20	1 40	1 80	1 160	1 320	Titre
Acute	+	o	o	o	o	o	1 10
Convalescent	+	+	+	o	o	o	1 40

+ = complement fixation o = no complement fixation

RASH PRODUCING VIRUS INFECTIONS (EXANTHEMATA)

The virus usually spreads in the blood stream producing a generalised constitutional upset before it localises in various organs Cutaneous eruptions are sufficiently distinctive in form and distribution to permit accurate clinical diagnosis without resort to laboratory confirmation In fact these self sufficient clinical characteristics may have been a factor in impeding our knowledge of the causative agent and its mode of spread

SMALLPOX (Variola)

The virus of smallpox probably enters the body through the respiratory mucosa and following multiplication spreads through the body in the blood eventually reaching the skin to produce a characteristic sequence of lesions

There is an abrupt prodromal stage of fever malaise headache and generalised aches suggesting a phase of viraemia At the same time a transient erythema may develop in a bathing trunks distribution and there may be petechiae and convulsions After three days of this non specific illness macules appear on the face forehead and scalp spreading centrifugally to the wrists and hands then the trunk and finally the legs and feet The rash tends to be most dense in areas distant from the umbilicus and most sparse on the trunk Within a day the small pink macules become papular and two days later become multilocular vesicles The prodromal pyrexia of about 103 F falls during this eruptive stage but rises again when the vesicles become secondarily infected with bacteria to form pustules Nowadays chemotherapy controls this bacterial invasion and so minimises the permanent scarring which used to follow the eruption Variants of this picture include the profuse and widespread lesions termed confluent smallpox, and the usually fatal haemorrhagic type Secondary bacterial invasion may also lead to bronchopneumonia but this responds to chemotherapy

The clinical picture may be modified by previous vaccination in such instances the prodromal stage may be absent and the typical lesions are not only sparse and superficial but they progress through the different stages more quickly Laboratory confirmation of the diagnosis may then be indispensable

Diagnosis (Table 11)

The virus can be *cultivated* on the chorioallantoic membrane of the twelve-day chick embryo Vesicular or pustular material is

Typical result (after Horsfall, 1950)

Serum	1 10	1 20	1 40	1 80	1 160	Titre
Acute	S	D	D	D	D	1 10
Convalescent	S	S	S	S	D	1 80

S = animals surviving
D = animals died

There is a significant increase in titre indicating a rise in antibody in convalescent compared with acute phase serum

INCLUSION BODIES

Certain virus infections are characterised by the presence of inclusion bodies which may be found in infected tissues during life or at autopsy (Table 12) They may be intranuclear or intra cytoplasmic, and acidophilic or basophilic in their staining character

TABLE 12—*VIRUS INFECTIONS INCLUSION BODIES*

Disease	Intra nuclear	Intra cytoplasmic	Tissue in which found	Staining characters
Chicken pox	+	Occasionally	Skin lesions	Acidophilic
Smallpox		+	Skin lesions	Acidophilic
Herpes zoster	+	Occasionally	Skin lesions	Acidophilic
Herpes simplex	+		Skin lesions nerve cells	Acidophilic
Rabies		+	Nerve cells	Acidophilic
Yellow fever		+	Liver cells	Acidophilic
Psittacosis		+	Alveolar exudate hilar lymph nodes Kupffer cells spleen	Basophilic
Lymphogranuloma venereum		+	Buboes	Basophilic
Inclusion conjunctivitis		+	Conjunctiva of lower tarsus	Basophilic; Matrix shows positive glycogen stain
Trachoma		+	Conjunctiva of upper tarsus	Basophilic; Matrix shows positive glycogen stain

of greater purity has become available It has the advantage of remaining potent when kept even at 45 C for up to two years

Vaccination is performed by placing a drop of lymph on the cleansed skin and scratching the skin through it

The following reactions may occur

In the *susceptible* individual a red papule develops on the fourth day and passes through the vesicular to the pustular stage by the ninth day It then dries up scabs and eventually scars There may be some fever and regional lymphadenitis

TABLE 13 —DIFFERENTIAL FEATURES OF SMALLPOX AND CHICKEN POX

	Variola (Smallpox)	Varicella (Chicken pox)
Incubation period	12 days	12 16 days
Prodromal symptoms	Severe	Mild or absent
Distribution of rash	Commences face forehead and scalp spreading to hands then trunk and legs	Commences back and chest
Density of lesions	Exposed areas	Unexposed areas
Evolution of lesions	3rd day—papules 5th day—vesicles 8th day—pustules 15th day—scabbing	1st or 2nd day—papules vesicles and pustules present in crops Scabbing soon follows
Vesicles	Multilocular	Unilocular
Cultivation of virus in chick embryo	Chorioallantoic membrane	No
Cultivation of virus in tissue culture	?	Yes
Stained smears from base of vesicles	Numerous small elementary bodies	Giant multinucleated cells
Inclusion bodies	Intracytoplasmic	Intranuclear
Complement fixation test using vesicle fluid as antigen	Specific reaction with anti vaccinial serum	No reaction with anti vaccinial serum
Serum antibodies	Demonstrable	Not yet practicable
Mortality	High	Negligible
Vaccination	Successful	Unnecessary

usually used for inoculation but blood from the prodromal stage has also given positive results Lesions are sought on the chorio-allantois after three days incubation and the specificity confirmed by microscopy of the membranes Specific anti vaccinial rabbit serum may be observed to protect infected eggs and finally, infected egg tissue may be used as antigen in a complement fixation test When performed in a laboratory accustomed to these techniques a result is available in about three days The isolation of virus from the blood after the second day of illness indicates a bad prognosis

Stained smears prepared from scrapings of the base of vesicles show enormous numbers of elementary or *Paschen bodies* This is useful in the early stage before pustule formation, it can be performed in any laboratory, and a result may be obtained within one hour

Acidophilic intracytoplasmic inclusions (*Guarnieri bodies*) may be seen in epithelial cells of the skin at the edge of vesicles and in lesions of the mucous membrane (Table 12) They are also observed in the infected chorioallantoic membrane of the chick embryo

Fluid from vesicles or pustules and scrapings from papules and crusts may be used as antigen in a *complement fixation test* with anti vaccinial serum A result is to be expected in twenty four hours Variola virus antigen may also be found in the blood early in the disease if present the outlook is always fatal

Serological antibodies develop in the course of infection and a rising titre is demonstrated by a complement fixation test using antigen prepared from rabbit vaccinial lesions A rising titre indicates recent infection but the presence of antibodies in the acute phase blood may be indicative of vaccination in the previous year

Prophylaxis

Following Jenner s (1798) observation that cowpox protected against smallpox, immunisation by means of the vaccinia virus of cowpox has been most successful in the control of smallpox Until recently such vaccination was compulsory

The vaccinia and variola viruses have a strikingly similar antigenic make up and they are immunologically identical The vaccinia virus used for vaccination is passed alternately in the skin of the rabbit and sheep or calf to maintain a satisfactory degree of potency Lymph collected from the vesicles maintains its potency for several months if kept at temperatures below 0°C It can also be prepared by cultivation in bovine tissue cultures Recently a dried vaccine

chromatin granules and nucleoli are absent Stained by Giemsa s method the nuclei contain reddish violet stringy amorphous material and green melanin granules are seen in a blue staining cytoplasm (Table 12) They are not seen in smallpox but they also occur in herpes zoster and herpes simplex

Treatment

The mild nature of the disease and life long immunity conferred by it have provided little impetus for any large scale attempts at prophylaxis with modified varicella vesicle fluid

Antibiotics do not influence the chicken pox virus although they minimise the secondary bacterial complications in the skin and respiratory tract

HERPES ZOSTER (Shingles)

Although the clinical features of herpes zoster and chicken pox are dissimilar there is much evidence to suggest that the causative virus is the same or at least closely related The following are suggestive points of similarity

Epidemiology The relationship of the two diseases is closer than could be explained by chance alone Varicella often leads to herpes zoster in adult contacts Some human transmission experiments using zoster vesicle fluid produced varicella in the recipients

Clinical The appearance of the vesicles and their subsequent evolution are similar although the distribution is localised in herpes zoster

Histology Acidophilic intranuclear and occasional intra-cytoplasmic inclusion bodies occur in both diseases (Table 12) The same giant multinucleated epithelial cells are found in the base of vesicles in zoster and chicken pox

Morphology Elementary bodies obtained from vesicle fluid in both conditions appear identical in size and shape when examined by electron microscopy

Host range There is the same lack of pathogenicity for animals

Serology A close cross serological relationship is demonstrable The elementary bodies of zoster or varicella can be agglutinated by convalescent zoster or varicella sera and similarly close relationships have been shown by complement fixation tests

Cytopathogenic effects in tissue cultures are similar

The virus of herpes zoster involves the sensory root ganglia of the spinal cord or of the cranial nerves causing an acute inflammation

In the *previously immunised* person a vaccinoid reaction may be present by the second day This is an accelerated response in which a milder and more superficial lesion develops more rapidly

A minimal or no response may indicate *complete immunity* but it is wiser to repeat the vaccination with a fresh batch of lymph before accepting this conclusion

There are rare but definite complications to vaccination They include severe local sepsis generalised vaccinia and post vaccinial encephalitis Because of the danger of local tetanus infection dressings are avoided after vaccination

Treatment

The variola virus is not vulnerable to antibiotics although the secondary bacterial complications are controlled Convalescent smallpox serum has been tried but has not proved life saving in severe infection

CHICKEN POX (Varicella)

Although the elementary bodies of the varicella virus have been demonstrable for over twenty years propagation of the virus has been extremely difficult This has been accomplished recently by tissue culture techniques

Although the causative viruses are quite unrelated the clinical features of chicken pox and smallpox may be confusingly similar Points of distinction are tabulated (Table 13)

Chicken pox is a mild disease of world wide distribution Its highly contagious nature suggests a respiratory portal of entry, it is prevalent in the relatively susceptible under fifteen years age group

Little more than a mild constitutional upset may precede the characteristic rash This appears most densely on the trunk and the lesions on the extremities are sparse Even in the mildest cases lesions are apparent in the axillae and the oral mucosa The stages of macules papules vesicles pustules and scabbing evolve in chicken pox in crops so that in twenty four hour all tages are evident at the same time in the same area

Diagnosis

Laboratory confirmation of the clinical diagnosis is rarely sought unless there is initial confusion with smallpox

Stained smears taken from the base of the vesicles show en larged giant, multinucleated epithelial cells in which the normal

chromatin granules and nucleoli are absent Stained by Giemsa's method the nuclei contain reddish violet stringy amorphous material and green melanin granules are seen in a blue staining cytoplasm (Table 12) They are not seen in smallpox but they also occur in herpes zoster and herpes simplex

Treatment

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Antibiotics do not influence the chicken pox virus although they minimise the secondary bacterial complications in the skin and respiratory tract

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Cytopathogenic effects in tissue cultures are similar

The virus of herpes zoster involves the sensory root ganglia of the spinal cord or of the cranial nerves causing an acute inflammation

with necrosis and lymphocytic infiltration The symptoms and signs are usually confined to the skin segment corresponding to this nerve root

A mild prodromal constitutional upset may be associated with pain in the affected cutaneous segment This is succeeded by the characteristic vesicular eruption restricted to the involved segment it is often unilateral The clinical picture is virtually unmistakable The vesicles evolve through the stages of pustules scabbing and eventual scarring as in chicken pox Troublesome neuralgia may persist in the typical sensory nerve distribution The most commonly involved areas are trunk, face and eyes, or arms Muscular paresis is rare but it may involve the corresponding motor pathways of ophthalmic and facial zoster

The condition may be precipitated by injuries drugs or radio therapy These examples of symptomatic herpes zoster have led to the suggestion that the virus is dormant in the nerve ganglia until provoked by these stresses

Diagnosis is essentially clinical although the procedures outlined for varicella are also applicable

Treatment The virus of herpes zoster is unaffected by antibiotics Any benefit is due to their influence on the secondary bacterial complications

HERPES SIMPLEX

The virus of herpes simplex is unrelated to that of herpes zoster despite the resemblance in terminology It can be cultivated readily in animals and on the chorioallantoic membrane of the chick embryo it also produces inclusion bodies (Table 12) and cytopathogenic effects in tissue cultures The ease of culture of the causative agent and detection of serological antibodies has enabled the natural history of the disease to be worked out in population surveys Infection only occurs in susceptible individuals without circulating antibodies Maternally transferred antibodies usually protect the infant up to six months Initial infection usually occurs in childhood when close contact provides ready dissemination of the virus It may be *asymptomatic and so passes unrecognised* although occasionally there may be a severe systemic infection with an acute stomatitis meningoencephalitis and liver and kidney lesions These profound changes indicate a stage of viraemia With recovery the patient develops circulating antibodies and becomes a carrier of the virus which remains dormant in the buccal mucosa He is now

subject to recurrent attacks of localised mucocutaneous blisters usually on the lips Circulating antibodies are usually sufficient to prevent a further generalised illness These local recurrences may also appear on the vulva and provide a source of infection to the newborn or they may recur in areas of chronic eczema (*Kaposi s varicelliform eruption*) Recurrences are not by any means universal but are liable to be provoked by intercurrent infections sunlight or other precipitating factors Carriers are always liable to transmit infection to susceptible individuals who have no circulating antibodies These are usually children because adults are either immune to reinfection or their more resistant epithelial surfaces are sufficiently protective

Diagnosis

Diagnosis is clinical but it may be confirmed by isolation of the virus by inoculation of animals or of the chorioallantoic membrane of the chick embryo with vesicle fluid saliva cerebrospinal fluid faeces or blood Cytopathogenic effects are noted in tissue culture Serological complement fixing and neutralising antibodies develop during convalescence and may persist throughout life A soluble herpes simplex antigen has been used to demonstrate dermal hypersensitivity (Table 24)

Treatment

The herpes simplex virus is unaffected by antibiotics although secondary bacterial invasion of the vesicles may be minimised

MEASLES

The causative virus has not hitherto been well recognised because of the difficulty in finding a susceptible animal host The disease has been transmitted to monkeys and to human volunteers and more recently the virus has been cultivated in tissue cultures

The virus readily infects susceptible children by the respiratory tract where it multiplies and eventually circulates in the blood This sequence corresponds to the prodromal respiratory catarrhal stage which is followed by the diffuse and characteristic rash

The catarrhal stage resembles a heavy cold but in addition there is fever and photophobia and Koplik spots appear in the buccal mucosa The latter appear like grains of salt and are surrounded by inflamed mucosa

The Koplik spots disappear before the rash commences on the fourth

day of illness as small discrete pink macules behind the ears and on the neck and forehead It spreads rapidly to the face trunk and limbs and then coalesces and deepens in colour to become a diffuse, blotchy deep red papular eruption Whereas the initial macules fade on pressure the confluent papules fail to yield or they become purple This is eventually followed by a coarse branny desquamation

The viraemic stage of the disease may also be marked by generalised lymphadenopathy and meningoencephalitis

Diagnosis (Table 11)

If necessary, the clinical diagnosis may be confirmed by isolation of the virus by tissue culture methods using nasopharyngeal washings or blood taken early in the disease

During convalescence serum antibodies develop which neutralise cytopathogenic effects in tissue cultures Complement fixing antibodies may be demonstrated against antigen prepared from kidney tissue culture

Prophylaxis

Prevention or attenuation of the disease is afforded by a 12 per cent solution of gamma globulin prepared from pooled adult serum It is only indicated in sick infants in whom the additional burden of measles would affect their prognosis adversely The dose varies whether the child is under 1 year (3 ml) aged 1 to 3 years (3 6 ml) or over 3 years of age (3 9 ml)

If the disease is prevented by a large dose there is no permanent immunity so the child is liable to contract measles at a later date A modified form of the disease attenuated by a smaller dose of gamma globulin confers some immunity although this may not be life long

Treatment

The measles virus is unaffected by antibiotics but the bacterial bronchopneumonia which used to be a devastating feature of the disease should be treated by an appropriate antibiotic Sulphona mides and antibiotics are unnecessary as a prophylactic measure in children suffering an attack of measles of ordinary severity

RUBELLA (German measles)

Animals are not susceptible to the causative virus but trans mission has been successful in human volunteers It has been

isolated from nasopharyngeal secretions and from the blood The probable portal of entry is the respiratory tract with eventual haematogenous dissemination and localisation in the skin

The mild prodromal upper respiratory tract infection and cervical lymphadenitis are followed by a generalised macular rash starting on the face and head and spreading downwards to the trunk The illness is altogether milder and of shorter duration than measles and there are no Koplik spots

Although usually a benign infection of childhood the occurrence of rubella in the first trimester of pregnancy is of serious significance because it may be followed by stillbirths or the birth of a deformed infant Foetal abnormalities include acyanotic heart disease microcephaly and mental deficiency cataracts and deafness These have been sufficiently frequent for some authorities to recommend therapeutic abortion when rubella complicates early pregnancy

Diagnosis

There are no laboratory tests to confirm the clinical diagnosis which is usually self-evident The lymphopenia with relative lymphocytosis is a feature common to all virus infections

Treatment

Treatment is symptomatic because the virus is unaffected by antibiotics The prophylactic value of gamma globulin remains unproven

RESPIRATORY TRACT VIRUSES

INFLUENZA

There are three immunologically distinct types of influenza viruses A B and C causing an identical clinical picture (p 137) The influenza A virus undergoes gradual antigenic changes over the years and this has led to the recognition of several somewhat similar substrains in various epidemics The plasticity of the A type is greater than that of B and by comparison influenza C virus is stable These observations are significant if any vaccination programme is contemplated (p 138)

Diagnosis (Table 11)

The virus may be isolated from sputum or throat washings which are inoculated into the amniotic cavity of the chick embryo The harvested fluid if infected with influenza virus has the capacity to

agglutinate various animal red blood corpuscles Further egg passages are necessary before the result can be said to be negative The strain of virus can be typed with specific influenza anti era

The patient s serum antibodies increase during convalescence They include haemagglutination inhibiting, complement fixing and neutralising antibodies

THE COMMON COLD

In 1930 the causative agent of this commonplace infection was successfully transmitted to human volunteers and chimpanzees, but despite intensive subsequent research it still remains uncultivated and unidentified (p 138)

ADENOIDAL-PHARYNGEAL-CONJUNCTIVAL (A P C) OR ADENOVIRUSES

Apart from influenza and the common cold there remains a nebulous group of non bacterial upper respiratory tract infections, probably caused by many different viruses Some are clinically indistinguishable from the common cold others are associated with pharyngitis tracheitis and conjunctivitis By means of tissue culture techniques several new viruses have been unmasked from tonsillar and adenoidal tissue They are currently segregated into eleven immunological types and collectively termed adenoviruses The previous nomenclature adenoidal pharyngeal-conjunctival (A P C) agents indicated the anatomical sites from which they had been recovered They grow readily and produce cytopathogenic effects in tissue culture but they are non pathogenic for laboratory animals or fertile eggs They produce type specific neutralising and group specific complement fixing antibodies These viruses are heat labile ether resistant and antibiotic insensitive

Type 4 (or the RI 67 strain) adenovirus is commonly associated with epidemics of acute febrile upper respiratory infections Types 3 and 7 adenoviruses have been causally related to pharyngitis with conjunctivitis whereas type 8 has been linked with epidemic keratoconjunctivitis

Diagnosis (Table 11)

Diagnosis of infection due to these agents may be made by isolation of the agent from nasopharyngeal washings or conjunctival scrapings in tissue culture Serum antibodies neutralise cytopathogenic effects in tissue culture These antibodies are type specific

whereas complement fixing antibodies in the serum are common to the whole group

PSITTACOSIS VIRUS

This is one of a group of large viruses (about 300-450 mμ) approaching the size of and sharing certain features in common with rickettsiae Other members of this group include the viruses of lymphogranuloma venereum trachoma and inclusion conjunctivitis as well as a large number of pneumonia producing viruses isolated from animals and man Like rickettsiae this group of viruses produce elementary bodies which may be stained by Castaneda s formol methylene blue and visualised by the ordinary microscope (Table 12) Furthermore they resemble rickettsiae in their susceptibility to antibiotics Neither of these is a feature of true viruses However rickettsiae require an arthropod host whereas viruses including the psittacosis family do not have one Thus the psittacosis group of viruses may be regarded as midway between the rickettsiae and viruses in their behaviour The psittacosis virus grows readily in the chick embryo guinea pig and mouse In view of a common antigen serological complement fixation tests are positive for all members and they cannot be distinguished in this way

Psittacosis may present as an acute respiratory tract infection (p 145)

NEUROTROPIC VIRUSES

POLIOMYELITIS

There are three immunologically distinct types of poliomyelitis virus *Since they do not confer cross immunity second attacks of* poliomyelitis due to a different strain are possible All three types must be incorporated in any effective vaccine

During epidemics the virus has been recovered from flies and cockroaches food faeces and sewage These may be links in the spread of infection with a gastro-intestinal portal of entry as in dysentery Its prevalence in summer months may be due to the increased facility of spread by these vectors A high standard of sanitation in a community tends to defer infection until adult life when it may appear in the form of explosive epidemics

After its ingestion the virus probably multiplies in the oropharynx and small intestine Early in the disease virus is recoverable from the pharynx and faeces and continues to be present in the latter for several

weeks Its mode of spread to the central nervous system is unknown It may traverse nerve fibres to reach the anterior horn cells, but at this stage virus has been recovered from the blood Both pathways may convey the virus to the central nervous system

Clinically inapparent infection is probably the commonest type and this provides the patient with lasting immunity Clinical types of infection may be grouped

Abortive poliomyelitis The patient suffers a minor illness with no characteristic features There is fever malaise headache sore throat or mild gastro-enteritis Poliomyelitis is only suspected if the paralytic form of the disease is endemic at the same time The constitutional upset suggests a stage of viraemia

Aseptic meningitis with meningism and photophobia Several agents are liable to produce this clinical picture (p 160) and poliomyelitis virus is strongly suspected as the cause if paralytic poliomyelitis is also prevalent in the community

Paralytic poliomyelitis due to anterior horn cell involvement by the virus Flaccid paralysis in some muscle group may be associated with painful spasm in others Paralysis is maximal within a few days of the onset and recovery as far as it will occur is usually complete within about six months

Bulbar poliomyelitis due to involvement of the cranial nerve nuclei and medulla This is a serious form of the disease because involvement of the respiratory centre leads to respiratory failure

Diagnosis (Table 11)

Virus isolation from throat swabs taken early in the disease or from faeces throughout the illness is practical now that the virus can be grown in various human and monkey tissue culture systems (including non nervous tissue indicating that it is not strictly neurotropic)

Serum antibodies Complement fixing antibodies are titrated against antigens prepared from infected tissue cultures Neutralising antibodies inhibit the cytopathogenic effects of tissue cultures

The cerebrospinal fluid contains an increase of leucocytes initially polymorphonuclear and later lymphocytic The protein content is a little elevated but the sugar level is normal (Table 18)

Prophylaxis

The Salk vaccine is a formalin inactivated preparation from infected monkey tissue cultures Following intramuscular inocula

tion there is a rise in serum antibodies which may be sufficient to protect against paralytic poliomyelitis However dead vaccines may only provide transient immunity and it is not yet known for how long they are effective They also carry the very slight risk that formalin inactivation may be incomplete An attenuated living virus vaccine may provide more lasting immunity Avirulent variants of the poliomyelitis virus have been incorporated in an oral vaccine which is now under clinical trial Gamma globulin protects against the paralytic form of the disease by preventing spread of the virus to the nervous system This protection only lasts about one month following the injection

Treatment

Antibiotics have no effect against the poliomyelitis virus By the time the patient has become paralysed he has already developed a reasonably high level of serum antibodies passive immunisation with convalescent serum or gamma globulin is therefore superfluous

Treatment of the non paralytic form of the disease is symptomatic Special precautions must be taken in the disposal of faeces nurses should be taught to regard even the mildest form of the disease in the same light as a virulent dysentery

In the paralytic forms treatment is best undertaken in special centres under conditions of co operative team work involving physician orthopaedic surgeon anaesthetist and physiotherapist The emphasis falls upon different members at various stages of the disease

RABIES

The causative agent of rabies is a large virus 100 to 150 milli microns in diameter which passes through filters with difficulty It has a wide host range including all mammals and many birds but experimental infection is commonly studied in mice rabbits guinea pigs hamsters or the chick embryo It is primarily a disease of dogs and wild carnivores human infection is the accidental complication of bites of animals whose saliva contains the virus The naturally occurring virus which involves canine salivary glands is termed the *street virus* when it has been adapted to laboratory animals by serial intracerebral passage the modified strain is referred to as *fixed virus*

Once inoculated into man by a severe bite the street virus traverses peripheral nerves to reach the central nervous system

weeks Its mode of spread to the central nervous system is unknown It may traverse nerve fibres to reach the anterior horn cells but at this stage virus has been recovered from the blood Both pathways may convey the virus to the central nervous system

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Prophylaxis

The Salk vaccine is a formalin inactivated preparation from infected monkey tissue cultures Following intramuscular inocula

Hyperimmune serum for passive immunisation should be used immediately after the patient has sustained severe lacerations from an animal in whom rabies is suspected but not proved This is followed by active vaccination when animal rabies has been confirmed

LYMPHOCYTIC CHORIOMENINGITIS

The lymphocytic choriomeningitis virus about 50 millimicrons in diameter is the cause of endemic infections in many animals including mice and dogs It is possible that man is infected by contaminated food or dust from these sources but the portal of entry is unknown

It is probable that many individuals contract inapparent infections or they suffer only a mild non specific pyrexial illness or an influenza like syndrome Following an incubation period of a few days viraemia may be followed by meningeal localisation causing aseptic meningitis (Table 18)

Diagnosis (Table 11)

Since it is impossible to differentiate the various causes of benign aseptic meningitis clinically the diagnosis of lymphocytic choriomeningitis rests on laboratory evidence

Isolation of the virus from spinal fluid or blood which is inoculated intraperitoneally into guinea pigs or intracerebrally into mice

Serum antibodies Complement fixing antibodies reach diagnostic levels towards the third or fourth week and neutralising antibodies develop two or three months after the onset The latter persist for several years and they are the more useful in routine serological surveys of populations

Cerebrospinal fluid shows a more marked pleocytosis than other varieties of aseptic meningitis except possibly that due to glandular fever The cell count ranges up to 3 000 cu mm of which 98 per cent are lymphocytes The spinal fluid protein value is raised and the sugar level is sometimes reduced but these features are of no differential diagnostic value

Treatment There is no specific chemotherapy and treatment is symptomatic

ARTHROPOD BORNE ENCEPHALITIS

Several neurotropic viruses of about 15 to 30 millimicrons in diameter some interrelated immunologically cause infections in

Following a variable incubation period up to several months various neurological manifestations develop including hyperaesthesia excessive salivation and increased muscle tone leading to convulsive spasms and opisthotonos Spasmodic contractions of the muscles of deglutition are precipitated by the act of swallowing or even following the sight of water, hence the alternative name hydrophobia

Rabies is characterised by hyperexcitability of the central nervous system and maniacal behaviour followed by terminal paralysis exhaustion and death

Diagnosis (Table 11)

The clinical suspicion is entertained by a history of an animal bite and should be confirmed when possible by an examination of the dog as well as the patient The dog should be isolated for two weeks if it has rabies this will become obvious by its abnormal behaviour increasing excitability and finally by its death within about ten days Post mortem examination of brain tissue particularly the pyramidal cells in the hippocampus reveals eosinophilic intracytoplasmic inclusions (*Negri bodies*) (Table 12) If these characteristic lesions are not found a brain suspension should be inoculated intracerebrally into mice and Negri bodies sought in the mouse brain tissue

The virus should be sought in the patient s saliva after it has been treated with antibiotics to eliminate bacterial contamination The saliva is inoculated intracerebrally into mice whose brains are examined for Negri bodies a few days later

In the course of infection and after vaccination complement fixing and neutralising antibodies develop in the patient s serum

Treatment

Strict quarantine measures for canines entering Great Britain have virtually eradicated the disease in this country This is fortunate since there is no specific chemotherapy If rabies is strongly suspected fourteen consecutive daily injections of a phenol inactivated rabbit brain vaccine should be administered Before deciding upon this course it is important to weigh up the chance of developing rabies against the small but definite risk of post vaccinial allergic encephalitis and paralysis Since this complication is due to an adverse antigen antibody reaction it is possible but not proven that it may be minimised by the cortisone group of drugs (p 223)

Hyperimmune serum for passive immunisation should be used immediately after the patient has sustained severe lacerations from an animal in whom rabies is suspected but not proved This is followed by active vaccination when animal rabies has been confirmed

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Since it is impossible to differentiate the various causes of benign aseptic meningitis clinically the diagnosis of lymphocytic chorio meningitis rests on laboratory evidence

Isolation of the virus from spinal fluid or blood which is inoculated intraperitoneally into guinea pigs or intracerebrally into mice

Serum antibodies Complement fixing antibodies reach diagnostic levels towards the third or fourth week and neutralising antibodies develop two or three months after the onset The latter persist for several years and they are the more useful in routine serological surveys of populations

Cerebrospinal fluid shows a more marked pleocytosis than other varieties of aseptic meningitis except possibly that due to glandular fever The cell count ranges up to 3 000 cu mm of which 98 per cent are lymphocytes The spinal fluid protein value is raised and the sugar level is sometimes reduced but these features are of no differential diagnostic value

Treatment There is no specific chemotherapy and treatment is symptomatic

ARTHROPOD BORNE ENCEPHALITIS

Several neurotropic viruses of about 15 to 30 millimicrons in diameter some interrelated immunologically cause infections in

Following a variable incubation period up to several months various neurological manifestations develop including hyperaesthesia excessive salivation and increased muscle tone leading to convulsive spasms and opisthotonos Spasmodic contractions of the muscles of deglutition are precipitated by the act of swallowing or even following the sight of water, hence the alternative name hydrophobia

Rabies is characterised by hyperexcitability of the central nervous system and maniacal behaviour followed by terminal paralysis exhaustion and death

Diagnosis (Table 11)

The clinical suspicion is entertained by a history of an animal bite and should be confirmed when possible by an examination of the dog as well as the patient The dog should be isolated for two weeks if it has rabies this will become obvious by its abnormal behaviour increasing excitability and finally by its death within about ten days Post mortem examination of brain tissue particularly the pyramidal cells in the hippocampus reveals eosinophilic intracytoplasmic inclusions (*Negri bodies*) (Table 12) If these characteristic lesions are not found a brain suspension should be inoculated intracerebrally into mice and Negri bodies sought in the mouse brain tissue

The virus should be sought in the patient s saliva after it has been treated with antibiotics to eliminate bacterial contamination The saliva is inoculated intracerebrally into mice whose brains are examined for Negri bodies a few days later

In the course of infection and after vaccination complement fixing and neutralising antibodies develop in the patient s serum

Treatment

Strict quarantine measures for canines entering Great Britain have *virtually eradicated the disease in this country This is fortunate* since there is no specific chemotherapy If rabies is strongly suspected fourteen consecutive daily injections of a phenol inactivated rabbit brain vaccine should be administered Before deciding upon this course it is important to weigh up the chance of developing rabies against the small but definite risk of post vaccinial allergic encephalitis and paralysis Since this complication is due to an adverse antigen antibody reaction it is possible but not proven that it may be minimised by the cortisone group of drugs (p 223)

OPHTHALMIC VIRUSES

TRACHOMA

The trachoma virus is about the same size as the psittacosis lymphogranuloma group of viruses (about 300 mμ) also common to this group are typical inclusion bodies which are found in the conjunctiva The virus has been transmitted to monkeys but not to other laboratory animals this has hampered knowledge of the causative organism of the disease Trachoma is characterised by follicular hypertrophy of the conjunctiva and pannus formation in the cornea leading to scarring and destruction of the eyelids and cornea Its insidious development is punctuated by acute inflammatory episodes due to secondary bacterial infection It is prevalent under conditions of poor nutrition overcrowding and in dry dusty areas all of which favour rapid spread of the disease by close direct contact or by flies It is a common infection of the Middle and Far East

Diagnosis (Table 11)

Laboratory confirmation of the diagnosis can be made by conjunctival smears which are stained by Giemsa s method to reveal the characteristic intracytoplasmic inclusion bodies (Table 12)

Complement fixing antibodies common to trachoma inclusion conjunctivitis psittacosis and to lymphogranuloma venereum may be present in low titre because all these viruses belong to a common family However they are of no diagnostic value in trachoma

Treatment

The tetracyclines and chloramphenicol are effective in controlling the disease partly because of their efficacy against secondary bacterial invasion and in part due to some success against the causative virus Oral administration should be reinforced by frequent local instillation into the conjunctival sac

INCLUSION CONJUNCTIVITIS

The causative virus like that of trachoma belongs to the psittacosis family It is of the same size has similar inclusion bodies common serum antibodies and the same limited host range as the trachoma virus It causes an acute follicular conjunctivitis but unlike trachoma it is more prone to involve the lower eyelid and does not involve the cornea with pannus formation and permanent scarring

vertebrates By the bite of infected arthropod vectors principally mosquitoes or ticks, man becomes an accidental host and develops an acute inflammation of the brain and spinal cord The various causative viruses include St Louis Eastern and Western equine Venezuelan equine Japanese B Murray Valley Russian spring summer West Nile and also the only one so far recognised in Great Britain the louping ill virus of sheep

Specific diagnosis cannot be made on clinical grounds because the picture may be indistinguishable from poliomyelitis and other types of meningo-encephalitis For accurate proof the causative virus may be isolated from the brain tissue of fatal cases or by the demonstration of serum neutralising antibodies (Table 11) There is no specific treatment

HEPATITIS VIRUSES

The hepatitis viruses have not yet been adequately identified nor cultured although there is some recent preliminary evidence that propagation in tissue culture may be possible Efforts to isolate the causal agent of hepatitis have failed through lack of a susceptible laboratory animal and current knowledge is based on the results of experiments in human volunteers From these human transmission experiments there is strong evidence that at least two agents are concerned Whether they are different viruses or different strains of the same virus remains to be determined Virus IH is identified with the syndrome of infective hepatitis occurring sporadically or in epidemic form and having an incubation period of two to six weeks Virus SH is identified with the syndrome of serum hepatitis which characteristically develops eight weeks to six months after parenteral inoculation of the virus in blood plasma or infected instruments

The virus of infective hepatitis is present in the blood and faeces of sufferers during the immediate pre icteric and the icteric phase of the disease It usually disappears during convalescence although a healthy carrier state may occur The virus of serum hepatitis is present in the blood during the long incubation period and may persist for as long as five years after apparent recovery The faeces unlike that in infective hepatitis does not carry the virus

Infection with either infective hepatitis or serum hepatitis guards against reinfection with the homologous virus but there is no cross immunity between the two viruses

The pathology of serum and infective hepatitis is identical (p 188)

Treatment

There is no specific chemotherapy and treatment is largely symptomatic Oral prednisolone is of value in alleviating painful orchitis

INFECTIOUS MONONUCLEOSIS (Glandular fever)

No aetiological agent has been isolated a viral cause is presumed by its infectious nature the absence of causative bacteria the lack of response to chemotherapy and by some inconclusive human and monkey transmission experiments The protean clinical manifestations include a general constitutional upset evidence of reticulo-endothelial involvement with *lymphadenopathy and splenomegaly* rashes sore throat meningo-encephalitis and jaundice

Diagnosis

Clinical diagnosis may be confirmed in the laboratory

Leucocyte count Early in the disease there is a leucopenia with a relative lymphocytosis but later it is followed by a leucocytosis due to an increase in the lymphoid series The distinctive glandular fever cell is a large mononuclear cell with foamy or deeply basophilic cytoplasm It is not unique to infectious mononucleosis because it has been observed in lesser degree in other acute virus infections

Paul Bunnell test This serological test is positive in about 70 per cent of patients by the second week of the disease but it may be positive in the first few days It consists in the demonstration of heterophile antibodies which agglutinate sheep erythrocytes The blood of normal individuals and especially those who have received horse serum injections may also contain sheep red cell agglutinins These agglutinins may be differentiated by guinea pig kidney or beef erythrocyte adsorption

Adsorbed by	*Infectious mononucleosis*	*Serum sickness*	*Normal serum*
Guinea pig kidney	—	+	+
Beef erythrocytes	+	+	—

These heterophile antibodies may be present in the spinal fluid of patients with infectious mononucleosis

In the newborn inclusion conjunctivitis is contracted from the infected genital tract of the mother during delivery In the adult, infected fingers may be a means of transmission of the virus from the genital tract to the eyes

Diagnosis (Table 11)

Conjunctival smears of the lower lid are likely to reveal inclusion bodies (Table 12) Complement fixing antibodies cannot be used to differentiate this condition from trachoma because the two viruses have similar antigenic properties

Treatment As for trachoma

MISCELLANEOUS VIRUS INFECTIONS

MUMPS

The mumps virus has a diameter of about 100 to 200 millimicrons It can be cultivated in the amniotic sac of the chick embryo and in the mouse hamster and monkey The portal of entry in man is probably the mouth or respiratory tract Following an incubation period of seventeen to twenty one days there is swelling of the parotid glands and pain on movement of the jaw A constitutional upset may precede it suggesting a stage of viraemia in the course of which the virus spreads to other tissues causing orchitis oophoritis mastitis pancreatitis or meningo encephalitis

Diagnosis (Table 11)

The clinical diagnosis is usually self evident Laboratory con firmation of the diagnosis may be sought when the parotid swelling is confused with bacterial parotitis or in order to determine the cause of meningo encephalitis which cannot be differentiated on clinical grounds

Isolation of the virus may be attempted from the saliva or cerebro spinal fluid early in the disease by cultivation in the chick embryo Its presence in the amniotic fluid is revealed by haemagglutination and specific antiserum neutralisation tests The virus may also be cultivated in tissue cultures

Serological tests include complement fixing haemagglutination inhibiting and neutralising antibodies

A skin test employs mumps antigen prepared from infected allantoic fluid (Table 24)

acidophilic inclusion bodies (*Councilman bodies*) (Table 12) In areas where the disease is endemic, specimens of liver tissue should be collected from fatal febrile illnesses of ten days duration or less This method provides proof of the disease in many instances in which it would otherwise be overlooked

Treatment

There is no specific chemotherapy Death results from renal damage so measures should be directed along the lines adopted for renal failure The stage of shock hypotension and oliguria should be combated by a regime similar to that recommended for tubular necrosis

Prevention of the disease consists in vaccination and the control of mosquitoes The 17D strain of virus attenuated by mouse brain or chick embryo passage is used in the preparation of a vaccine of proven value A single inoculation is followed, within seven to ten days by antibodies which persist for at least six years It has proved successful in the control of epidemics and as protection to inhabitants or travellers in endemic zones Aerial travel has increased the necessity for vigilance and travellers should be vaccinated at least ten days before arrival in equatorial Africa or South America It should not be given concomitantly with primary smallpox vaccination, but either three days beforehand or three weeks after a successful smallpox take

LYMPHOGRANULOMA VENEREUM

This is closely related to the psittacosis virus They are the same size and have a similar developmental cycle communal antigenic properties provoke the development of similar complement fixing antibodies Although this might provide confusion in the interpretation of diagnostic serological tests the clinical features are quite different in the two diseases

Diagnosis (Tables 11 and 23)

The clinical diagnosis of lymphogranuloma venereum may be confirmed by isolation of the virus from smears of the ulcer or from bubo pus which is inoculated into the yolk sac of the chick embryo *Complement fixing antibodies* develop two or three weeks after the onset of the primary vesicle The *Frei test* is a helpful intradermal method (Table 24 and p 214) for confirming the diagnosis

Treatment (p 215) is discussed with venereal infections

Treatment

There is no specific chemotherapy and treatment remains symptomatic The symptoms of the severely ill patient may be alleviated by oral prednisolone, its administration may be considered if there is evidence of severe meningo encephalitis

YELLOW FEVER

The yellow fever virus is small measuring about 20 millimicrons in diameter It is transmitted to man by the bite of infected mosquitoes The virus cycle is a direct human one in urban yellow fever but wild monkeys may be an intermediate reservoir of infection in the jungle variety The two common endemic regions are South America and equatorial Africa The virus is both viscerotropic and neurotropic In the course of serial intracerebral passages in mice it loses its viscerotropism by prolonged passage in tissue culture an attenuated strain 17D is suitable for vaccination The virus produces intranuclear acidophilic inclusion bodies (*Councilman bodies*) which are occasionally found in human liver cells and are observed in the livers of infected monkeys

The clinical features of yellow fever are principally due to involvement of the liver kidneys and heart Following an incubation period of three to six days a constitutional upset with fever prostration and vomiting is associated with shock and hypotension jaundice haemorrhages albuminuria and relative bradycardia Delirium proceeds to coma and death within about nine days If there is recovery the temperature becomes normal within this time and convalescence progresses rapidly and completely There are no sequelae and life long immunity follows Apart from the classical course described the majority of infections are probably milder with no detectable jaundice and only a few constitutional symptoms

Diagnosis (Table 11)

The virus may be isolated from the blood early in the disease by intracerebral inoculation of mice which develop encephalitis if the virus is present

Neutralising antibodies develop early in the course of infection

Post mortem evidence of the disease is best seen in the liver which is yellow and fatty The hepatic cells undergo severe, diffuse non inflammatory necrosis most evident in the mid zones of the lobules Scattered irregularly through these areas are distinctive intranuclear

blood of both patients during convalescence and the agent itself induced paralysis in new born suckling mice Reports soon followed of the isolation of the Coxsackie viruses in patients with paralytic and non paralytic poliomyelitis aseptic meningitis pyrexia of unknown origin gastro-enteritis the Guillain Barré Landry syndrome epidemic pleurodynia and herpangina The ubiquitous nature of this family of viruses led to a spurious association between them and a variety of diseases but a more cautious attitude has now been adopted in relating the Coxsackie viruses to human disease They resemble the poliomyelitis viruses in size resistance to antibiotics their prevalence during summer months and in their occurrence in the oropharynx and faeces The mode of spread of infection and portal of entry are also similar to poliomyelitis

The four clinical infections at present most frequently related to the Coxsackie viruses are epidemic pleurodynia herpangina aseptic meningitis and neonatal myocarditis

Epidemic pleurodynia (Bornholm disease)

Bornholm is an island off the coast of Denmark During 1930 its inhabitants were stricken by an epidemic of myositis which was variously referred to as devil s grip epidemic myalgia or Bornholm disease It had undoubtedly occurred in earlier times it was observed in Iceland in 1856 and termed pleurodynia It has been recognised in both epidemic and sporadic forms as an acute febrile self limiting infection characterised by lower intercostal muscle pain or diaphragmatic pleurisy occasionally accompanied by pleural friction The pain may be aggravated by such simple respiratory excursions as sniffing and it may also account for diminished movements of the chest weak breath sounds and a high diaphragm which may appear immobile and in spasm The pain subsides in two to three days but transient relapses may occur a few days or even a month later

Herpangina

This condition has also been termed vesicular or aphthous pharyngitis It is a summer illness of early childhood characterised by yellowish white vesicles or ulcers surrounded by a red areola on the soft palate and faucial pillars Since the herpes simplex virus can also cause vesicular stomatitis it is unfortunate and confusing that the term herpangina is perpetuated in association with the Coxsackie viruses

SANDFLY FEVER

The sandfly fever virus is small mea uring about 20 millimicrons in diameter It is transmitted to man by the bites of female sandflies which have become infective by feeding on patients Following an incubation period of two to six days the patient experiences a sudden onset of malaise headache, photophobia meningism or a gastro intestinal upset Since there are no specific features, sandfly fever can only be suspected clinically in new arrivals to tropical or sub tropical areas during the season of this particular vector The causative virus may be isolated from the patient s blood early in the illness by mouse inoculation (Table 11) Neutralising antibodies develop during convalescence There is no specific treatment Childhood infection in the indigenous population confers lifelong immunity

DENGUE

The causal virus is about the same size as the virus of sandfly fever (20 mμ) One species of mosquito Aedes aegypti feeds on patients and spreads infection by biting exposed individuals particularly susceptible new arrivals to endemic tropical zones Following an incubation period of five to nine days there is a sudden constitutional upset with rigors fever prostration headache painful eyeballs and severe backache The character and severity of widespread muscle and joint pains have been responsible for the synonym *breakbone fever* There may be scarlatiniform morbilli form or petechial rashes lymphadenopathy and splenomegaly

Diagnosis is essentially clinical although it is possible to demon strate neutralising haemagglutinin inhibiting and complement fixing antibodies in the convalescent serum of patients (Table 11)

There is no specific *treatment* symptomatic measures should be employed for the relief of pain and discomfort The prevention of dengue demands intensive anti mosquito programmes of control and the use of mosquito repellents by exposed and susceptible persons

COXSACKIE VIRUS INFECTIONS

Coxsackie is a village on the banks of the Hudson river in upper New York State In the course of investigating an outbreak of poliomyelitis there during 1948 a hitherto unrecognised filterable agent was isolated from the faeces of two children with lower limb paralysis Neutralising antibodies for this new virus appeared in the

PART 3

INFECTIONS OF SYSTEMS

Aseptic meningitis

The Coxsackie virus should be considered in the differential diagnosis of the many causes of this syndrome (p 160 and Table 18)

Neonatal myocarditis

The Coxsackie viruses should be suspected as a cause of myocarditis in infants, particularly if Bornholm disease is prevalent in the community at the same time These viruses should also be considered as a possible cause of acute myocarditis before it is dismissed as 'idiopathic

Diagnosis (Table 11)

The features of Bornholm disease in its epidemic form are sufficiently striking to permit a confident clinical diagnosis It should be borne in mind in the differential diagnosis of sudden severe pain in the chest or abdomen simulating perforation of a peptic ulcer or appendix biliary or renal colic and myocardial infarction The diagnosis of Coxsackie virus infection cannot be made with such clinical certainty in the other forms of illness and laboratory confirmation must be sought

Isolation of the virus is possible from throat washings spinal fluid or faeces The virus is cultivated in suckling mice or tissue culture Based on the pathological findings in infected mice the Coxsackie viruses have been classified into two Groups A and B Group A viruses are responsible for herpangina and Group B for epidemic pleurodynia aseptic meningitis and myocarditis

Serological evidence is given by the development of neutralising or complement fixing antibodies during convalescence A significant rise in specific neutralising antibodies provides good evidence of recent infection The complement fixation test is less reliable since one strain of virus may provoke a non specific rise of complement fixing antibody to an unrelated strain

Treatment

The Coxsackie viruses are resistant to all known chemotherapy so treatment is symptomatic Infections due to these agents are benign and self limiting and do not appear to leave permanent sequelae

CHAPTER 12

RESPIRATORY SYSTEM

UPPER RESPIRATORY TRACT INFECTIONS

UPPER respiratory tract infections involve the nares oropharynx, tonsils sinuses or larynx and may spread to the trachea bronchi and lungs The causative organisms are bacteria viruses or a combination Pathogenic bacteria include *Dipl pneumoniae Str pyogenes Staph aureus* and *H influenzae* Viruses known to cause acute upper respiratory tract infections are the *influenza* viruses and the adenoidal pharyngeal-conjunctival (A P C) or *adenoviruses* The *common cold* is probably viral although the agent has not yet been isolated Improved techniques will undoubtedly reveal other viruses causing upper respiratory infections

Virus infections render the tissues of the upper respiratory tract more vulnerable to secondary bacterial invasion Depending upon the virulence of the invading organisms and the defences of the host the infection is limited to the upper respiratory tract or may descend to the lung substance causing bronchopneumonia of varying severity

INFLUENZA

Infection by the influenza viruses is airborne causing a febrile illness with constitutional symptoms of malaise headache and generalised aching these may overshadow mild upper respiratory tract symptoms Poor general health or lack of specific immunity may lead to a more severe illness complicated by broncho pneumonia Although the influenza virus may invade the alveoli causing patchy consolidation and a true virus pneumonia secondary bacterial invasion is by far the commonest cause of the broncho-pneumonia The constitutional symptoms of uncomplicated influenza usually subside in three days but lung changes may persist clinically and radiologically for two weeks

When the influenza virus and Staph aureus attack the respiratory mucosa the infection may be fulminating with a high mortality Autopsy reveals a haemorrhagic tracheo-bronchopneumonia

Diagnosis

This is usually clinical but it will not differentiate influenza from other types of upper respiratory tract infection Laboratory

The diagnosis is based on the clinical features for there is no laboratory means of confirmation

Treatment is symptomatic Antibiotics have no effect against the common cold virus but they are helpful in minimising secondary bacterial infection which contributes to troublesome sinusitis purulent bronchitis or even bronchopneumonia

TABLE 14—COMPARISON OF INFLUENZA AND COMMON COLD

	Influenza	Common cold
Fever	Moderate	Minimal
Constitutional symptoms	Marked	Mild
Coryza	Mild	Marked
Virus isolated	Yes	No
Serological antibodies	Yes	Not demonstrable

NASOPHARYNGITIS DUE TO ADENOVIRUSES

The term febrile catarrh has been used to describe a group of upper respiratory tract infections some of which are due to adenoviruses This corresponds to acute undifferentiated respiratory disease in the American literature Clinical features include nasopharyngitis, laryngitis tracheitis and conjunctivitis or the picture may be indistinguishable from influenza or the common cold Serological surveys suggest that infection with the adenoviruses is widespread and that most adults may have been previously infected with one or more types

Diagnosis is suggested clinically and confirmed by isolation of the viruses using tissue culture techniques and by demonstration of specific serum antibodies (Table 11)

Treatment Infection with these agents is a benign self limiting disease for which there is no specific chemotherapy

PERTUSSIS (H pertussis)

Whooping-cough is an acute highly infectious disease of the respiratory tract characterised by an emetic cough and a distinctive whoop presumably due to the irritative endotoxin liberated by H pertussis on the respiratory epithelium The incubation period is seven to fourteen days The causative organism *Haemophilus pertussis* is abundantly present in the respiratory tract during the early catarrhal stage but less obvious during the subsequent spasmodic paroxysmal stage

confirmation consists in isolating the influenza virus from sputum or throat washings and demonstrating a significant rise in specific serum antibodies during convalescence (Table 11)

Prophylaxis

There is no cross immunity among the A B and C influenza viruses Since it is impossible to predict which type of influenza epidemic is imminent or even distinguish the type clinically an effective vaccine should be expected to protect against all strains If this were the limit of the problem a planned immunisation programme would be feasible Unfortunately, influenza A virus gradually changes its antigenic pattern over the years Fresh epidemics due to new strains, not incorporated in any previous vaccine make their appearance It is difficult to keep the potency of any vaccine abreast of these changes By the time the new strain has been isolated typed and incorporated in a vaccine the epidemic has subsided

Formalin inactivated polyvalent vaccines are prepared from infected allantoic fluid A good serum antibody response follows single subcutaneous injections and protection follows if the epidemic is due to a strain covered by the vaccine

An efficient vaccine excites an adequate antibody response at the site of virus invasion In the case of influenza high antibody levels are desirable in the superficial respiratory mucosa It is possible that means of encouraging local antibody production may prove more effective than the present methods of systemic immunisation

Treatment

Antibiotics do not affect the influenza viruses but they are of use in minimising secondary bacterial invasion For the mild uncomplicated virus infection symptomatic measures suffice If the illness has a fulminant onset and particularly if a concomitant staphylococcal infection is suspected, an antibiotic is given directly specimens of sputum or nasopharyngeal washings have been taken When necessary the patient may also need treatment for anoxia and peripheral circulatory failure

COMMON COLD

The clinical picture differs from influenza (Table 14) dominant symptoms being sneezing and a nasal discharge at first watery but later thick and purulent due to secondary bacterial invasion

maintained by occasional booster doses during childhood It is best combined with diphtheria immunisation

BACTERIAL PNEUMONIA

Infection may be due to *Dipl pneumoniae Str pyogenes Staph aureus Myco tuberculosis* or to the Gram negative organisms *K pneumoniae* and *H influenzae* It is rarely due to *B anthracis Past pestis* or *Past tularense* Pneumonia may be lobar or broncho pneumonic Aspiration pneumonia is a localised bronchopneumonia with collapse and consolidation of a bronchopulmonary segment following aspiration of material usually infected mucus from the upper respiratory tract An aetiological is more satisfactory than an anatomical classification since it focuses attention on specific chemotherapy (Table 15)

Pneumococcal pneumonia remains the commonest type of simple pneumonia although because of preceding chemotherapy the causal agent is not always isolated Pneumococci of types I II III IV and VII are associated with more severe infection than the higher types In the days of serum treatment typing of the organism was an important investigation This is no longer necessary since all types are uniformly sensitive to penicillin

Streptococcal pneumonia was a frequent cause of death during the 1919 world influenza pandemic It continues to be a common bacterial invader associated with virus infections of the respiratory tract particularly in elderly or undernourished subjects

Staphylococcal pneumonia The organism reaches the lungs from the blood stream by inhalation from the upper respiratory tract or by local spread from below the diaphragm When complicating septicaemia abscess formation occurs rapidly and often involves both lungs When Staph aureus reaches the lung by inhalation bronchopneumonia may proceed to necrotic abscess formation Severe bronchiolitis causing valvular blockage may result in distension of these abscess cavities producing a characteristic radiological picture of soap bubble cysts The severe and fatal staphylococcal tracheo-bronchopneumonia accompanying influenza virus infections is often unhalted by antibiotics suggesting an exalted virulence due to the synergistic action of bacteria and virus Hyaluronidase production by Staph aureus may contribute to spread of infection

Tuberculous pneumonia may be associated with tuberculous bron chitis with cavitation or with caseous lymph nodes It should be

Diagnosis

In typical pertussis the diagnosis can be made confidently on clinical grounds However previous vaccination may confer incomplete immunity, resulting in difficulty in recognising the mild modified outbreaks Laboratory help may be derived from

Isolation of the organism during the first week of illness The patient coughs on a Bordet Gengou plate or a nasopharyngeal swab is cultured on this medium Penicillin is incorporated to prevent overgrowth of other respiratory tract bacteria

Serology Complement fixing and agglutinating antibodies develop during convalescence Serum should be taken during the acute phase as well as during convalescence to detect a rising titre Previous immunisation may be reflected in a demonstrable level of antibodies in the early acute phase specimen of blood

A skin test (Table 24) similar to the tuberculin test but using pertussis agglutinogen reveals previous infection This is of only limited use for it is only of diagnostic value from the third week of the disease It is useful in surveys of the susceptible population

Treatment

H pertussis is sensitive *in vitro* to the tetracyclines and chloramphenicol but the clinical infection responds only moderately well to these antibiotics The difficulty in evaluating results is understandable in a disease with such a variable course and in which the mechanical factor of bronchiolar plugs of tenacious mucus is so important When administered in the *early* catarrhal stage within a week of symptoms tetracycline can be expected to reduce the severity of the paroxysms of whooping and to minimise complications due to secondary pyogenic cocci Since the disease is characterised by an emetic cough oral administration of the antibiotic may present practical difficulties If a palatable oral suspension cannot be retained tetracycline should be administered intravenously or intramuscularly

Gamma globulin, obtained from persons who have had repeated pertussis vaccination may confer temporary passive protection or modify the course of the disease when given sufficiently early by the intramuscular route in doses of 2 5 ml every other day for one week

Prevention

Active immunisation should be performed by three monthly injections of 1 ml pertussis vaccine during the first year of life and

suspected particularly in the racially susceptible in the middle aged and elderly and whenever pneumonia does not respond promptly to penicillin or tetracycline

Klebsiella pneumonia (Friedlander s) is commoner in patients over the age of 40 years It may vary from the mildest illness to a ful minating infection with abscess formation It often complicates upper respiratory tract infections as an aspiration pneumonia which is penicillin resistant The sputum may be tenacious and blood streaked giving the appearance of a brick red emulsion of pus and blood

Other causes of bacterial pneumonia are all comparatively rare *Haemophilus influenzae* pneumonia in children is a rapidly developing diffuse bronchopneumonia often accompanied by obstructive laryngitis There may be an associated leucopenia Apart from this overwhelming infection of childhood the precise role of H influenzae is uncertain for it is often found in the normal respiratory tract in a variety of chronic pulmonary infections and also accom panying virus infections of the respiratory tract

B anthracis pneumonia Inhalation of the spores of B anthracis may cause an acute bronchopneumonia A history of occupational exposure to hides wool or similar animal products is usually elicited

Pasteurella pneumonia is due to Pasteurella pestis or to Past tularense The organism is inhaled by contact with the discharges or carcases of infected rats (plague) or rabbits and hares (tularaemia)

Diagnosis of bacterial pneumonias

Diagnosis is established clinically and confirmed by isolating the causal organism from the sputum and blood (Table 15) Chest radiographs are helpful in following the course of the disease

Treatment

Penicillin is effective in pneumococcal streptococcal and in B anthracis pneumonia as well as certain instances of staphylococcal infection If Staph aureus is resistant in turn to penicillin and tetracycline it is then advisable to use erythromycin novobiocin or vancomycin preferably in combination

Other bacterial pneumonias are sensitive to streptomycin In the treatment of tuberculous pneumonia this is given in single daily injections and combined with isoniazid or P A S Anti tuberculous chemotherapy is continued for at least one year In the treatment of K pneumoniae H influenzae and Pasteurella infections strepto-

TABLE 15 —BACTERIAL PNEUMONIAS

Causal organism	Clinical features	Organism isolated from	Treatment
Diplococcus pneumoniae (pneumococcus)	Usually lobar	Sputum Blood	Penicillin
Streptococcus pyogenes	Often bronchopneumonia in elderly May accompany virus infections	Sputum Blood	Penicillin
Staphylococcus aureus	Septicaemia→multiple lung abscesses Bronchiolitis→radiological soap-bubble cysts With influenza virus→fulminating tracheo-bronchopneumonia	Sputum Blood	1 Penicillin } Domiciliary strain 2 Tetracycline } Domiciliary strain 3 Erythromycin+tetracycline } Hospital strain 4 Novobiocin+vancomycin } Hospital strain
Mycobacterium tuberculosis	May present as penicillin resistant pneumonia Occasionally extra thoracic tuberculosis	Sputum Laryngeal swab Gastric washings Bronchoscopic aspirate	Streptomycin and isoniazid or P A S
Klebsiella *pneumoniae* (Friedlander)	Commonly > 40 years *May present as penicillin* resistant pneumonia Tenacious red sputum	Sputum Blood	Streptomycin and sulphonamides or tetracycline o[r] chloramphenicol
Haemophilus influenzae	Obstructive laryngo-tracheitis especially infancy Often associated with virus infections	Sputum Blood	Streptomycin and sulphonamides or tetracycline Chloramphenicol if complicated by influenzal meningiti[s]
Bacillus anthracis	Woolsorter's lung	Sputum Blood Cutaneous pustule	Penicillin
Pasteurella pestis	Primary pulmonary } plague Septicaemic } plague Bubonic } plague	Sputum Blood Aspirate of buboes	Streptomycin and sulphonamides or tetracycline
Pasteurella tularensis	Pulmonary } tularaemia Oropharyngeal } tularaemia Cutaneous } tularaemia Abdominal } tularaemia Meningeal } tularaemia	Sputum Blood Spinal fluid Aspirate of buboes	*Streptomycin and sulphonamides or tetracycline*

pulmonary segments such as occurs with segmental aspiration pneumonia The radiological appearance may be that of diffuse miliary mottling

The leucocyte count is not raised but there may be a relative lymphocytosis This is a point of differentiation from bacterial pneumonia although it is quite non specific and holds for all virus infections

This syndrome may occur in psittacosis Q fever or cold haemag glutinin pneumonia Since the clinical picture is common to all three they may only be distinguished by laboratory means

PSITTACOSIS

The name is derived from the Greek word *psittakos* meaning parrot and was applied to this disease because infection was considered to have been transmitted by birds of the order Psittaci formes In its widest sense the name parrot includes in this group the macaw cockatoo lorie and parakeet The domestic fowl duck and pigeon may also harbour the virus and so they are also potential reservoirs of human airborne infection The alternative term ornithosis is more comprehensive

The causative virus may be isolated from blood nasopharyngeal washings or from the lung at autopsy but it is more convenient to demonstrate a significant increase in serum antibody titre during convalescence (Table 11)

Q FEVER

This virus pneumonia is due to Rickettsia (or Coxiella) burneti for which cows and sheep are a reservoir Infection is transmitted by tick faeces or by contaminated milk The rickettsia may be isolated from blood or nasopharyngeal washings or recent infection is demonstrated by a convalescent rise in serum antibodies

COLD HAEMAGGLUTININ PNEUMONIA

The causative agent (or agents) has not been isolated The claim that it is a virus pneumonia is largely based on the facts that no causative bacteria have been isolated in numerous epidemics human transmission experiments have suggested the presence of a filterable agent and the clinical features are indistinguishable from known virus pneumonias

In 1943 it was recognised that the sera of patients with this type of pneumonia agglutinated various animal red blood corpuscules at

mycin should be given by injection at least eight hourly and in addition an absorbable sulphonamide is given by mouth Treatment is continued for five to seven days depending on the response

Care should be taken in giving streptomycin to patients with penicillin resistant pneumonia lest underlying tuberculosis be masked and remains undetected If there is any doubt it is preferable to give tetracycline and if this proves ineffective consider bronchoscopy

In addition to specific chemotherapy the aspiration pneumonias are treated by postural drainage so that mucus plugging the bronchi is dislodged and aeration of the segment is promoted

VIRUS PNEUMONIAS

Infection of the lungs by a virus may occur in measles chicken pox and influenza but the pneumonia in these diseases is far more commonly due to secondary bacterial invasion and the accompanying clinical picture is usually distinctive

There remains a group of non bacterial pneumonias which are often buried in the meaningless term primary atypical pneumonia This refers to an acute pulmonary infection that does not conform clinically radiologically nor therapeutically to the accepted pattern of bacterial pneumonia It is suspected of being viral in view of its epidemic explosiveness fairly long incubation period for a respiratory tract infection and by its lack of response to sulphonamides or penicillin Confusion arises when the term primary atypical pneumonia is regarded synonymously with penicillin resistant pneumonia for it is apt to include aspiration bronchopneumonia or pneumonia associated with a neoplasm

Symptoms of a constitutional upset overshadow those of a respiratory disorder Headache chilliness malaise muscular pains and anorexia are associated with a slight dry cough retrosternal discomfort and pyrexia and a paucity of abnormal signs in the lung fields A pleural effusion is rare and its presence should question the diagnosis of a virus pneumonia The pulse may be slow especially in relation to the degree of fever Sputum if present is commonly mucoid and contains only commensals It may be blood streaked but it is not rusty as in bacterial pneumonia

There is no pathognomonic radiological appearance The extent of the opacity is surprisingly out of proportion to the few abnormal physical signs The opacity is ill-defined ground glass in density and most important need bear no precise relation to the broncho-

malaise Within twenty four hours there is a lowering of the fever and the temperature is usually normal in forty-eight hours Many reports of the ineffectiveness of chemotherapy may be due to clinical confusion with aspiration pneumonia (Table 16) for which antibiotics have mixed success

TABLE 16 —DIFFERENTIAL DIAGNOSIS OF VIRUS PNEUMONIA AND ASPIRATION PNEUMONIA

	Virus pneumonia	Aspiration pneumonia
Onset	Constitutional	Upper respiratory tract infection
X ray finding	Not necessarily segmental	Segmental lesion
Complement fixation test for psittacosis Q fever or influenza	May be +	—
Cold haemagglutinins	+	—
Streptococcus MG agglutinins	+	—
Response to sulphonamides and penicillin	Poor	Moderate to good
Response to tetracycline	Good	Variable
Response to postural drainage	None	Good

EMPYEMA

A collection of pus in the pleural cavity may complicate pneumonia intrapulmonary or subphrenic abscess mediastinitis from a ruptured oesophagus or penetrating wounds of the chest Infection is usually due to one or more of the organisms causing pneumonia

Diagnosis

The clinical diagnosis is confirmed by chest radiography and pleural aspiration The specimen should be examined grossly and also by direct microscopy for cells and bacteria and by culture on appropriate media, including anaerobic conditions if such organisms as Actinomyces israeli are suspected Guinea pig inoculation is essential if tuberculosis is suspected The fluid may be sterile if preceding chemotherapy has been given

Treatment

Systemic chemotherapy should be reinforced by intrapleural instillation if it is considered that the agent does not readily diffuse into the pleural cavity or the presence of thick fibrinous exudate

a temperature of 0° 5° but not at room temperature This observation made it possible to define this type of pneumonia The agglutinin is thermo stable and is found in the gamma globulin fraction

Cold haemagglutinins usually appear during the second week of illness and decline after the fourth week Their presence may be extremely transient and this could account for the variable estimates of their frequency in different epidemics The more severe the illness the higher is the cold haemagglutinin titre Very high titres may cause haemolytic anaemia and jaundice through intravascular clumping of red cells by auto-agglutination Blood grouping errors are liable to occur and a blood group AB result may be falsely due to these agglutinins When blood is taken from the patient agglutination may be detected on the rim of the syringe barrel or it may be suspected because of difficulty in performing a blood count

Cold haemagglutinins have been observed in many diseases apart from pneumonia They may occur in reticuloses hepatic cirrhosis haemolytic anaemia trypanosomiasis and associated with Raynaud s syndrome However this does not lessen their diagnostic usefulness for virus pneumonia is the only acute infection of the respiratory tract in which they occur in a significant titre On rare occasions they have been observed in low titres in bacterial pneumonias

A further serological test which distinguishes this type of pneumonia is based on the presence of circulating agglutinins to an indifferent streptococcus the streptococcus MG (The ability of the serum to agglutinate an apparently irrelevant non haemolytic streptococcus is reminiscent of the Weil Felix reaction which also depends on the non specific agglutination of a bacterium by the patient s serum) Agglutinins appear during the first week of illness but the maximum titre occurs towards the fourth week As with cold haemagglutinins the height of the titre bears some relation to the severity of the infection Antibodies against streptococcus MG are distinct from those which cause cold haemagglutination A combination of both tests yields a somewhat higher incidence of positives than either alone Serum should be collected as early as possible in the illness and again at weekly intervals A rising titre of these antibodies is more significant than high stationary levels

Treatment of virus pneumonias

The tetracyclines are effective in the treatment of psittacosis Q fever and cold haemagglutinin pneumonia Within a few hours there is a lessening in intensity of the headache chilliness and

CHAPTER 13

HEART

INFECTIVE PERICARDITIS

THE diagnosis of all types of pericarditis is suggested by a combination of praecordial pain pericardial friction tachycardia pyrexia and a characteristic electrocardiographic pattern Other distinguishing features depend upon the causal infection

Pyogenic pericarditis due to *Staph aureus Dipl pneumoniae* or *Str pyogenes* is now fortunately uncommon It is usually secondary to septicaemia or severe pneumonia distinctive features include the rapid development of a purulent pericardial effusion with a hectic temperature and a marked polymorphonuclear leucocytosis

Tuberculous pericarditis may be secondary to caseous mediastinal lymph nodes or to adjacent tuberculous pneumonia A straw coloured or blood stained lymphocytic effusion commonly develops Chronic constrictive pericarditis may be a sequel particularly if treatment is delayed

Mycotic pericarditis is extremely rare but may occur when actinomycosis blastomycosis or coccidioidomycosis is widely disseminated

Echinococcal cysts of the pericardium are also rare but they may be confused with other types of pericardial cyst The Casoni test and a specific complement fixation test are helpful in diagnosis (p 185)

Benign aseptic pericarditis has been attributed to a virus but no causal agent has yet been identified

Treatment

The early treatment of pyogenic pericarditis with the appropriate antibiotic should prevent the development of frank suppuration If this late stage is reached surgical drainage and local instillation of the antibiotic into the pericardial cavity is advisable

Vigorous and prolonged antituberculous chemotherapy with a combination of streptomycin isoniazid and P A S in successive courses for one year may prevent the development of late constrictive pericarditis although it is yet too early to be certain

INFECTIVE ENDOCARDITIS

Infective endocarditis may be due to circulating pyogenic organisms which cause an acute septicaemia ulcerative endocarditis

prevents this diffusion The drugs which diffuse into this cavity most readily are isoniazid and chloramphenicol, and less certainly the sulphonamides, penicillin and tetracycline Permeation is more likely with an acutely inflamed highly vascular pleura than in the presence of thickened fibrotic, avascular adhesions

When empyema is due to a Gram positive organism, penicillin in doses of 50 000 to 100 000 units should be deposited intrapleurally at the completion of each aspiration Larger doses are unnecessary *and may in fact excite a reaction with increase in the pleural fluid* Intrapleural penicillin need only be continued until sterility of the pleural cavity has been achieved The antibiotic of choice for other empyemas depends upon the sensitivity of the causal organism Tetracycline polymyxin bacitracin and neomycin may all be given by the intrapleural route In the treatment of tuberculous empyema oral isoniazid should always be used because of its ready diffusibility For a similar reason oral chloramphenicol is useful against a susceptible organism

When aspiration is difficult because of thick pleural contents, intrapleural streptokinase streptodornase may be used to liquefy thick pus It may be combined with the appropriate antibiotic Finally surgical intervention may be necessary for closure of a bronchopleural fistula for drainage or excision of an empyema pocket, or for decortication of the lung to permit its unimpeded re-expansion In the case of tuberculosis the operation of extra pleural pneumonectomy may be indicated when a destroyed lung lies beneath a chronic tuberculous empyema

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INFECTIVE ENDOCARDITIS

Infective endocarditis may be due to circulating pyogenic organisms which cause an acute septicaemia ulcerative endocarditis

and abscesses in various organs Alternatively it may show few or none of the features of a fulminant infection and this insidious variety is commonly referred to as subacute bacterial endocarditis Unlike the acute the subacute type is predominantly due to invasion by *Str viridans* or *Str faecalis* It is the more important of the two, because it is far more frequent and because its masquerades may defy detection until a stage when therapy is too late to be life saving The following features should arouse suspicion of subacute bacterial endocarditis in a patient with rheumatic or congenital heart disease or less commonly syphilitic aortic incompetence

1 The insidious development of fever, especially after dental or other manipulations when large numbers of oropharyngeal streptococci enter the blood stream
2 Embolic phenomena due to dislodgment of infected valvular clots into skin or nail bed, kidneys spleen brain or retina
3 Malaise loss of weight fatigue, anaemia or other evidence of a constitutional upset
4 Neurological signs or a frank cerebrovascular catastrophe in a young adult

Although some of these features may be absent any two together demand repeated blood cultures Treatment should not be delayed whilst awaiting a positive result Blood culture negative cases have a poorer prognosis and this has been attributed to the time wasted in attempting to obtain positive blood cultures at the expense of early treatment Deeply embedded foci of infection within protective clots on the heart valves may be associated with persistently negative blood cultures

Treatment

A dangerous expectant policy is avoided by the following routine although this may inadvertently (but harmlessly) encompass an occasional patient without subacute bacterial endocarditis

1 When a clinical diagnosis has been based on a combination of the above features three blood cultures are taken on the first day and again on the second day during a pyrexial phase *Little is to be gained by further cultures* because if they prove sterile during the first two days the chance of subsequent cultures being positive is small
2 On the second day, when blood culture specimens have been taken treatment is commenced with 2 million units of penicillin

daily in divided doses until the blood culture results become available If a sensitive organism is isolated and there is a gratifying clinical response this daily dose is continued until the patient has received 100 million units of penicillin Crystalline benzylpenicillin is given three hourly for three days after which administration may be continued by a long-acting penicillin combined with soluble penicillin once daily Organisms inhibited in vitro by 0 5 unit per ml should respond to this dosage

3 If the cultured organism is partially resistant to penicillin requiring up to 5 units per ml for in vitro inhibition daily doses of 10 000 000 units of penicillin are given

4 If blood cultures are negative daily doses of 5 000 000 units of penicillin are used This is empirical but it is dictated by the poorer prognosis of this group of cases

5 If in the course of the first week s treatment with penicillin pyrexia continues and fresh emboli appear then intramuscular streptomycin (2 g daily) should be given and penicillin dosage is increased to 20 million units daily This combination has proved effectively synergistic This combination should be used from the outset for enterococci and Gram negative bacilli It is wiser to embark on this combined course of treatment early rather than try to potentiate the blood level of penicillin by renal tubular blocking agents such as probenecid If a satisfactory clinical response is apparent the combined course should be continued for six weeks

6 When antibiotic sensitivity tests suggest that the organism is partially resistant to streptomycin and especially if this is supported by a poor clinical response intramuscular bacitracin (250 units/kg body weight every six hours) may be given with penicillin

7 The tetracyclines and chloramphenicol are poor substitutes and clinical results have been disappointing These bacteriostatic drugs should only be considered when the bactericidal drugs have failed It is vital that the organisms are killed otherwise the infection may recur Furthermore the bacteriostatic drugs should not be combined with such agents as penicillin and streptomycin *for there is a possible risk of antagonism in combination*

8 When active rheumatism coincides with bacterial endocarditis adrenocortical hormones should not be given for they may spread infection to other valves and depress important immuno logical mechanisms Salicylates provide a safer alternative

By following a planned programme of management, the control of infection in subacute bacterial endocarditis can usually be achieved. Despite this there still remains a substantial mortality rate due to heart or renal failure or thrombo-embolic complications. Relapse after apparently successful treatment is often attributed to a recurrence of infection, although it may be due to circulatory or renal failure. Autopsy findings alone prove that the septic process is healed.

INFECTIVE MYOCARDITIS

True infective myocarditis is infrequent, since the early and successful chemotherapy of pyogenic infections. Four groups of infective agents may invade the myocardium, namely viruses, rickettsiae, parasites and fungi. Both the poliomyelitis and Coxsackie groups of viruses are known to cause *virus myocarditis*, but other, as yet unidentified viruses may be still commoner causes of what is now regarded as 'idiopathic myocarditis'. There is no convincing evidence that influenza and the common cold are associated with a true virus myocarditis.

Rickettsial myocarditis is best exemplified by scrub typhus, whereas *parasitic myocarditis* may occur in trichiniasis, toxoplasmosis and trypanosomiasis. Theoretically, systemic dissemination of any fungus or yeast may cause myocarditis, but in practice, it is usually due to intrathoracic extension of actinomycosis to the pericardium and myocardium from an adjacent pleuropulmonary focus.

An oblique relationship exists between haemolytic streptococci and *rheumatic carditis* in that a hypersensitivity reaction to the products of this organism rather than a true septicaemia is responsible. *Diphtheritic myocarditis* is due to the toxin elaborated by Corynebacterium diphtheriae. In neither instance does the myocarditis result from direct bacterial invasion.

Treatment

Apart from bed rest and specific chemotherapy when available, peripheral circulatory collapse and cardiac failure must be prevented or treated.

SYPHILITIC AORTITIS

Within thirty years of primary infection, cardiovascular syphilis may appear as aortic incompetence or aortic aneurysm.

Diagnosis

This is established by suggestive clinical features of aortic involvement and possibly also by evidence of syphilis elsewhere such as in the nervous system Fluoroscopic evidence of a dilated aorta particularly in its ascending part should always be sought Serological tests for syphilis are positive in about nine tenths of patients and when available the treponema pallidum immobilisation test provides an even more sensitive index of past syphilitic infection

Treatment

It is questionable whether penicillin halts progression of the lesion but it is customary to administer a course of treatment as for syphilis elsewhere in the body (see p 212)

CHAPTER 14

CENTRAL NERVOUS SYSTEM

CLINICAL evidence of meningeal irritation demands lumbar puncture with examination of the cerebrospinal fluid for its pressure, cellular content protein and glucose levels and for organisms Meningism is not in itself a disease, but a symptom of several different conditions which mimic meningitis If the spinal fluid is under increased pressure but it is chemically and cytologically normal, then an extra meningeal infection should be sought to explain the meningism If however the cellular content is significantly increased a true meningeal infection is present

In children under 1 year of age, the classical signs of meningeal irritation may be absent but a lumbar puncture is indicated by evidence of alternating drowsiness and irritability vacuity of expres sion an odd high pitched cry an inexplicable pyrexia or bulging anterior fontanelles

ACUTE MENINGITIS

This is commonly due to the pyogenic organisms—*N meningitidis, Dipl pneumoniae Str pyogenes* and *Staph aureus*—and less commonly due to certain Gram negative bacilli—*Esch coli K pneumoniae Salmonellae Proteus* and *Pseudomonas pyocyarea* In children under the age of 3 years the causal agent may be encapsulated *type b H influenzae*

MENINGOCOCCAL MENINGITIS

Meningococcal meningitis may be associated with petechiae, purpura muscle and joint pains or adrenal cortical failure due to a fulminating septicaemia The turbid spinal fluid resembles ginger beer Stained films of this fluid reveal Gram negative diplococci The specimen should also be cultured and a precipitin test performed (p 86)

Treatment

The drug of choice is an absorbable sulphonamide because it traverses the blood brain barrier and reaches the purulent meningeal exudate rapidly (Table 17) It is given orally together with an

TABLE 17—TREATMENT OF BACTERIAL MENINGITIS

Organism	Treatment						Alternative treatment
	Oral 4 hourly	Days	Intramuscular (i m) or intravenous (i v)	Days	Daily intrathecal	Days	
N meningitidis	Absorbable sulphonamide 1 g	6	Thiasolucin 2 g i v	1	—		Intrathecal and i m penicillin
D pl pneumoniae Str p pyogenes Staph aureus	—		Penicillin 2 mega units i m daily	10	Penicillin 20 000 units	4	2 hourly penicillin i m , or i v and oral tetracycline
H influenzae	Chloramphenicol 0 25 g Absorbable sulphonamide 1 g	6	Thiasolucin 2 g i v	1	—		Intrathecal streptomycin and polymyxin
Esch coli K pneumoniae	Absorbable sulphonamide 1 g	6	Streptomycin 1 g i m 8 hourly	6	Streptomycin 2 mg / kg	4	Oral and i v tetracycline or intrathecal and i m polymyxin
Salmonella	Chloramphenicol 0 25 g	10	—		—		Oral and i v tetracycline
Ps pyocyanea	—		Polymyxin 2 mg /kg i m daily	6	Polymyxin adults 5 10 mg children 2 5 mg	4	—
Proteus	Novobiocin 0 5 g	6	Streptomycin 1 g i m 8 hourly	6	Streptomycin 2 mg / kg	4	Life saving measure —i m and intrathecal neomycin
Myco tuberculosis	Isoniazid 50 mg	180	Streptomycin 1 g i m daily	120	Streptomycin 2 mg / kg	7	Also Na P A S
Trep pallidum	—		Penicillin 1 mega unit daily	21	—		—

intravenous loading dose and treatment is continued for six days Penicillin may also be given for a fulminant infection

PNEUMOCOCCAL MENINGITIS

No condition better reflects the advances of antibiotic therapy during the last twenty years Until 1936 this infection was almost always fatal Nowadays early treatment with adequate intra muscular and intrathecal penicillin has reduced the mortality rate to virtually nil It may follow mastoiditis middle-ear disease or respiratory tract infections but in a minority of cases no primary focus of infection can be found The purulent turbid cerebrospinal fluid contains Gram positive cocci in pairs or short chains and from it pneumococcal polysaccharide may be precipitated by adding specific antiserum The latter may be a useful confirmatory test if previous penicillin therapy has masked the presence of pneumococci

Treatment

Intramuscular penicillin in doses of 2 000 000 units daily for ten days is reinforced by daily intrathecal penicillin for four days (Table 17) The latter is given in 10 ml saline in doses up to 25 000 units daily Some advocate an alternative regime of massive doses of intramuscular penicillin repeated every two hours through out the day and night and avoiding intrathecal penicillin because of its possible toxicity by that route However present-day crystalline preparations of benzylpenicillin are not toxic when given intrathecally and should cause no concern compared with the anxiety of under treatment The tetracyclines are also effective against pneumococci but they should not be combined with penicillin because of an antagonistic effect

STAPHYLOCOCCAL AND STREPTOCOCCAL MENINGITIS

These infections may complicate septicaemia due to respiratory tract or skin infections or meningitis follows trauma when there may be several infecting organisms As in other forms of pyogenic meningitis the cerebrospinal fluid is turbid and purulent Strep tococci are seen as chains whereas staphylococci occur in clusters

Treatment

The treatment of streptococcal meningitis is similar to that of pneumococcal meningitis (Table 17) If a satisfactory early response is not obtained or in vitro antibiotic sensitivity tests reveal that the

streptococci are partially resistant to penicillin intramuscular streptomycin in doses of 1 g eight hourly should be added If this combined treatment proves ineffective daily intrathecal bacitracin in doses of 10 000 units for adults (or 5 000 units for infants) is given for five days Oral or intravenous tetracycline may prove effective but it is a bacteriostatic agent and should only be considered when the bactericidal agents have proved ineffective

Staphylococcal meningitis may be resistant to antibiotic therapy especially if the disease has been contracted in hospital Antibiotic sensitivity tests should be performed as soon as possible Treatment is instituted with the broad spectrum antibiotic *in least current use in that particular hospital* This may demand the use of chloramphenicol or erythromycin with one of the newer anti staphylococcal agents such as novobiocin or vancomycin Intrathecal bacitracin is effective in the dose recommended for streptococcal meningitis The further management is dictated by the results of the sensitivity tests

If the infection was contracted away from hospital the immediate treatment is intramuscular and intrathecal penicillin as for pneumococcal meningitis until antibiotic sensitivity tests on the Staph aureus are known

HAEMOPHILUS INFLUENZAE MENINGITIS

This is due to the encapsulated type b organism It occurs principally in children under the age of three years by septicaemic spread from the respiratory tract The rarity of severe infections in adults is presumably due to naturally acquired immunity in childhood The turbid purulent cerebrospinal fluid contains Gram negative cocco-bacilli and also the specific capsular polysaccharide of the organism The presence of the latter is demonstrated by a simple precipitin test Specific type b antiserum is layered on spinal fluid and a precipitate is noted at the interface The organism may also be found in the nasopharynx and blood

Treatment

Early treatment is imperative to avoid sequelae such as subdural focal effusions or later neurological and psychiatric complications The rapid diffusibility of oral chloramphenicol into the cerebrospinal fluid makes it the drug of choice (Table 17) It has reduced the previously high mortality to negligible proportions The treatment of choice combines an absorbable sulphonamide with chloram

phenicol Both may be administered simultaneously by stomach tube if swallowing is difficult in the comatose patient Alternatively streptomycin may be combined with a sulphonamide but it is necessary to give the streptomycin intrathecally (-5 mg daily for four days) as well as intramuscularly Polymyxin is effective but this again should be given intrathecally If tetracycline is used treatment must be initiated by intravenous or intramuscular routes since its diffusion across the blood brain barrier following oral administration is unreliable Treatment with any of these drugs should be continued for up to one week

OTHER GRAM NEGATIVE ORGANISMS

These include *Esch coli K pneumoniae Salmonellae Pseudomonas pyocyanea* and *Proteus* which reach the meninges by septicaemic spread or following trauma or intrathecal injections

Treatment (Table 17)

Esch coli and K pneumoniae meningitis are treated with an absorbable sulphonamide together with intrathecal and intramuscular streptomycin or alternatively by intrathecal and intramuscular polymyxin If tetracycline is used its oral administration should be reinforced by its intravenous use for the first two or three days to ensure an adequate spinal fluid concentration

Salmonella meningitis responds to oral chloramphenicol It is rarely necessary to resort to parenteral administration but it may be given intramuscularly or by very slow intravenous infusion

Pseudomonas pyocyanea meningitis demands intramuscular and intrathecal polymyxin for there is no satisfactory alternative

Proteus meningitis is troublesome to control because of the relative insensitivity of this organism Some stains of Proteus are moderately sensitive to novobiocin which may be given orally at the same time as intrathecal and intramuscular streptomycin As a life saving measure the toxicity of neomycin may be disregarded and this drug should be given intramuscularly

SUBACUTE MENINGITIS

As distinct from acute pyogenic meningitis the onset is usually more insidious with increasing irritability and drowsiness possibly accompanied by changes of personality and behaviour and without treatment ending in coma Signs of meningeal irritation are initially

less prominent The causal organisms are *Myco tuberculosis* *Trep pallidum* and rarely *Torula histolytica*

TUBERCULOUS MENINGITIS

This is part of a generalised miliary tuberculosis with frequent evidence of thoracic or abdominal involvement and the presence of choroidal tubercles The clear or xanthochromic lymphocytic cerebrospinal fluid on standing develops a fibrin clot from which acid fast bacilli may be isolated The protein content of the fluid is increased and the glucose level is reduced below 50 mg /100 ml

Treatment

Early diagnosis and treatment with anti tuberculous drugs have revolutionised the prognosis of this condition which was previously nearly always fatal Oral isoniazid has proved invaluable for it diffuses rapidly into the cerebrospinal fluid making intrathecal administration unnecessary (Table 17) It is given in doses of 20 mg /kg for children or 3 8 mg /kg for adults for a minimum duration of six months It should be accompanied by intramuscular streptomycin in doses of 20-40 mg /kg daily for a similar period It is not yet certain whether oral isoniazid has made intrathecal streptomycin superfluous Until there is more evidence on this point intrathecal streptomycin should be given in doses of 25 to 50 mg daily for the first week and thereafter twice weekly for two months Oral P A S should be reserved for infections with tubercle bacilli showing partial resistance to the other drugs when all three anti tuberculous drugs appear desirable

If the patient fails to progress satisfactorily on the above regime and pneumoencephalography suggests the development of a hydrocephalus intrathecal tuberculin and/or prednisolone should be given in addition to the anti tuberculous drugs

SYPHILITIC MENINGITIS

This may occur in the secondary or tertiary stages of the disease The cerebrospinal fluid contains up to 200 cells per cu mm chiefly lymphocytes The spinal fluid Wassermann reaction is positive and the Lange curve is meningitic

Treatment One million units of a long acting penicillin is given intramuscularly every day for three weeks (Table 17) Intrathecal penicillin is unnecessary

TORULA MENINGITIS

This is a rare type of subacute meningitis due to blood borne dissemination of a fungus Torula histolytica (Cryptococcus neo formans) The insidiously developing meningitis is punctuated by remissions and relapses and it is associated with evidence of fungus involvement of the skin lungs, kidneys and other organs The cerebrospinal fluid protein is markedly elevated, and a moderate *pleocytosis consists of many mononuclear cells The spinal fluid* glucose content is normal or reduced The causative fungus is readily detected by direct microscopy in the spinal fluid (p 51)

Treatment is symptomatic some success has been claimed for actidione

ASEPTIC MENINGITIS (Table 18)

This syndrome consists of an acute meningitis in which the spinal fluid is predominantly lymphocytic and no causative bacteria can be isolated from it There is no adjacent suppuration to suggest secondary meningeal spread from infected sinuses middle ear disease or from the nasopharynx A normal cerebrospinal fluid glucose level is a common but not invariable feature and this is useful in distinguishing it from tuberculous meningitis Aseptic meningitis usually runs a benign self limiting course, and this is fortunate because there is no specific treatment

The cause usually remains undetermined although benign aseptic meningitis may sometimes be due to

1 Virus infection such as lymphocytic choriomeningitis mumps herpes simplex infectious mononucleosis poliomyelitis and the Coxsackie viruses or the new family of ECHO viruses
2 Bacterial meningitis may also present as a benign aseptic meningitis either when chemotherapy has been commenced in the prodromal stage or as a circumscribed but leaking brain abscess
3 Leptospirosis due to Leptospira canicola or less frequently Leptospira icterohaemorrhagiae
4 Spirochaetal infections due to Treponema pallidum or Borrelia recurrentis of relapsing fever
5 Arthropod borne virus meningoencephalitis Although several are recognised including Western Eastern and Venezuelan equine encephalomyelitis St Louis Japanese and Murray Valley

TABLE 18.—DIFFERENTIAL DIAGNOSIS OF SOME CAUSES OF ASEPTIC MENINGITIS

Cause	Clinical associations	C S F* cells/cu mm	Causative organism in	Serological tests
Lymphocytic choriomeningitis virus	Prodromal P U O Influenza-like illness	Up to 3 000	Blood C S F	Complement fixation Neutralising antibodies
Mumps virus	Parotitis Pancreatitis Orchitis Mastitis	Up to 1 000	Blood C S F Saliva	Complement fixation
Herpes simplex virus	Systemic infection with renal involvement	Up to 500	C S F	Complement fixation Neutralising antibodies
Glandular fever agent	Lymphadenopathy Tender spleen Sore throat Morbilliform rash Jaundice	Up to 3 000	—	Paul Bunnell
Poliomyelitis virus	Paralytic poliomyelitis in community Muscle tenderness	Rarely > 300	C S F Faeces	Complement fixation Neutralising antibodies
Coxsackie virus	Epidemic pleurodynia Herpangina	As for poliomyelitis		
ECHO virus	Sudden onset Rubelliform rash Epidemic in community	Up to 3 000	C S F Faeces Throat washings	Neutralising antibodies
Leptospira canicola	Conjunctival suffusion Muscle pains Jaundice	Up to 1 000	Blood Urine	Complement fixation Agglutination

*Cells predominantly lymphocytic glucose level usually over 50 mg /100 ml

encephalitis Russian spring summer encephalitis and louping ill only the latter is recognised in Great Britain

6 Post infection encephalomyelitis, complicating measles, varicella or rubella, or following vaccination for rabies or smallpox This group is distinctive since there is preceding or accompanying evidence of the causative exanthem The characteristic histological feature is widespread demyelinisation of the brain and spinal cord which distinguishes it from the preceding viral encephalitides

Treatment

This is largely symptomatic for these widely different conditions Among those listed (Table 18) only leptospirosis responds to specific chemotherapy with penicillin and even this condition must be recognised and treated at an early febrile stage

Incompletely treated bacterial meningitis a leaking brain abscess and spirochaetal infections are amenable to specific chemotherapy The demyelinating post infection encephalomyelitis group should be given the benefit of a trial of oral prednisolone

INTRACRANIAL ABSCESS

This is now a comparatively rare condition It is most commonly secondary to infection elsewhere in the body and this original focus commonly determines its intracranial site Middle ear infections lead to temporal lobe or cerebellar abscesses infections of the sinuses and face to the frontal lobe and respiratory tract infections may cause an abscess of the cerebral hemispheres Osteomyelitis of the skull and penetrating wounds may give rise to respectively extradural and deep intracranial abscesses

The invading organisms include *Staph aureus Str pyogenes Dipl pneumoniae* or *coliform* organisms or a mixed infection may also include organisms of the *Proteus* and *Pseudomonas* groups There are no characteristic features peculiar to any one organism although the type of organism often suggests the source or primary focus of infection

Treatment

Whenever feasible the abscess should be drained and instilled with an appropriate antibiotic and also with a radio-opaque medium to outline its extent The drugs which may be administered topically

are penicillin streptomycin tetracycline polymyxin and bacitracin any of these may be given locally through a catheter by slow infusion for prolonged effect In addition, the antibiotic chosen should also be given parenterally especially at the time of aspiration or extirpation of the abscess

CHAPTER 15

PERITONEUM AND INTESTINE

PERITONITIS

INFLAMMATION of the peritoneum is secondary to disease of one of the organs which it envelops Infection may be limited to an abscess in the area adjoining the infected viscus or it may be wide spread resulting in generalised peritonitis It follows perforation of any gastro intestinal ulcer inflamed appendix infected diverticulum carcinoma or empyema of the gall bladder or infection may spread from a diseased salpinx Cortisone therapy has increased the risk of perforation of an inflamed viscus and also by lowering the host s defences it may contribute towards severe peritonitis This is all the more serious since the peritonitis may remain unsuspected under the shield of cortisone for a few days The invading organisms are usually a mixture of Gram positive and Gram negative organisms representative of the intestinal tract flora

Tuberculous peritonitis of either the adhesive or ascitic type is now becoming increasingly rare It is more commonly seen in the racially susceptible and secondary to miliary dissemination or to caseous mesenteric lymph nodes Primary pneumococcal peritonitis is still rarer and is confined to the grossly under nourished

Diagnosis

The diagnosis of acute generalised peritonitis is readily suggested by hectic fever abdominal pain and tenderness muscular guarding vomiting and the development of paralytic ileus The more chronic forms with localisation of the infection by fibrous adhesions are less well recognised as instanced by subphrenic abscess pelvic peritonitis retro-caecal appendicitis or some types of tuberculous peritonitis When sepsis is suspected by the clinical signs by polymorphonuclear leucocytosis and possibly by accompanying radiological abnorma lities operative intervention and drainage is advisable The pus should be examined by direct microscopy culture and if indicated guinea pig inoculation

Treatment

When the causal organism is known the appropriate antibiotic should be given parenterally Peritoneal administration is given

only during surgery If the patient is shocked and collapsed the antibiotic should always be given intravenously with transfusion When the causal organism is unknown a mixed infection must be assumed and tetracycline is the drug of choice A 0 1 per cent solution should be freshly prepared every day and administered by drip transfusion in doses of 0 5 g twelve hourly

Tuberculous peritonitis demands oral isoniazid since it diffuses freely through the peritoneum and also intramuscular streptomycin Anti tuberculous chemotherapy should be continued for at least one year

The primary disease whether it be a perforated viscus typhoid fever or ulcerative colitis is treated along the appropriate lines local collections of pus are drained and in all instances a deranged fluid balance is corrected

INTESTINE

Infections of the gastro-intestinal tract may involve chiefly the small intestine or colon or both The symptoms vary according to the predominant site of infection the causal organisms and the acuteness or chronicity of the inflammation Intestinal infections may be classified as follows

- Acute gastro-enteritis
  - Food poisoning
  - Infantile gastro-enteritis
  - Staphylococcal enteritis
- Dysentery
  - Bacillary
  - Amoebic
- Enteric fever
  - Typhoid and paratyphoid
- Cholera
- Tuberculosis
- Helminthiasis

ACUTE GASTRO ENTERITIS

FOOD POISONING

Any sudden attack of vomiting and diarrhoea particularly in several people simultaneously in a community must always suggest food poisoning Classification is aetiological

Bacteria organisms or their toxins
Poisonous foods shell fish mushrooms rye bread
Chemical contamination including heavy metals and insecticides

Bacterial food poisoning due to the numerous types of salmonellae is by far the commonest The organism survives light cooking and often contaminates meat and eggs By contrast, the enterotoxin of Staph aureus and the spores of clostridia are heat resistant and survive

TABLE 19—FOOD POISONING

Cause	Staphylococcal enterotoxin	Salmonellae	Clostridium perfringens
Incubation period	1 to 4 hours	12 to 24 hours	8 to 22 hours
Onset	Vomiting Diarrhoea Prostration	Abdominal colic Diarrhoea	Abdominal colic Diarrhoea
Vomiting	Marked	Mild	Rare
Fever and constitutional upset	Uncommon	Common	Rare
Duration	Up to 24 hours	1 to 6 days	Up to 24 hours
Laboratory diagnosis	Staph aureus may be isolated from food *and from vomit* Association strengthened if they are of same phage type No satisfactory test for enterotoxin	Salmonella isolated from faeces Type *assigned by* agglutination tests with specific antisera or by specific bacteriophages	Organism isolated from food and *from faeces*
Chemotherapy	Nil	Oral chloramphenicol	Oral penicillin

cooking and processing Some clinical points may help to differentiate food poisoning due to toxin from that due to bacteria (Table 19) An onset within four hours of taking the suspected food strongly suggests ingestion of preformed staphylococcal enterotoxin Salmonellae and clostridia require longer to multiply in sufficient numbers in the intestine to produce enough toxin to cause symptoms Acute gastro-enteritis due to staphylococcal enterotoxin is heralded by marked vomiting prostration and collapse whereas bacterial

gastro-enteritis is more commonly associated with abdominal colic diarrhoea fever and a constitutional upset

Botulism is a distinctive type of food poisoning which is extremely rare in Great Britain The heat resistant spores of Cl botulinum germinate in improperly processed foods and produce a neurotoxin which causes neuromuscular inco ordination There is paralysis of eye muscles causing diplopia difficulty in swallowing and in speech and bulbar paralysis progressing to fatal respiratory failure These neurological features may be preceded by gastro enteritis The toxin in suspected foods can be typed by neutralisation with specific antitoxin in mice

In some outbreaks none of the usual bacterial causes can be identified It is possible that under certain circumstances various inhabitants of the normal intestine become pathogenic or alternatively a virus may be the causative organism

Management of an outbreak of food poisoning

1 An accurate history is essential in an effort to trace the source of infection This includes factors common to more than one case time of onset of symptoms types of food consumed and their source and also who ate and who did not eat these foods
2 All suspected foods specimens of vomit and of faeces should be saved for bacteriological examination
3 Food poisoning is notifiable and the local medical officer of health should be informed by telephone immediately Further manage ment is by the practitioner public health authorities bacteriologist and the hospital to which patients are admitted all working together as a team
4 Marked shock and collapse should be corrected by intravenous fluids Specific chemotherapy plays a secondary role to symptomatic relief An early bacteriological report will be helpful in choosing an appropriate antibiotic as for example chloram phenicol for salmonella infections However an antibiotic will not neutralise toxins which are causing symptoms it can only be expected to suppress further growth of organisms

Once neurological signs of botulism are apparent administration of specific antitoxin is probably too late Polyvalent antitoxin 50 000 units intramuscularly should be given to neutralise any unfixed toxin The patient should be tested for serum hypersen sitivity and if necessary desensitised

INFANTILE GASTRO ENTERITIS

Epidemics of vomiting and diarrhoea affecting the newborn or older infant may be associated with special serological types of Escherichia coli The important serotypes identified in Great Britain include those possessing the somatic O antigens 26 55 and 111 It is not clear whether these organisms are causative or whether they accompany some other as yet unrecognised invader possibly a virus Tissue culture techniques for virus identification may prove fruitful in the future

The disease varies in severity In the very acute case the onset is sudden with repeated vomiting and diarrhoea the stools rapidly becoming watery green and containing much mucus Dehydration and acidosis are profound the child becoming stuporose collapsed and oliguric The mortality varies with the severity of the infection and the efficacy of treatment but can be as high as 50 per cent

An isolated coliform colony is tested against a loopful of un diluted polyvalent Esch coli antiserum on a slide, and observed for the rapid development of coarse agglutination Pathogenic Esch coli do not exhibit this clumping in normal saline or acriflavine so it is convenient to check this preliminary slide agglutination in the presence of a loopful each of 0 85 per cent saline and of a 1 500 solution of acriflavine Further slide testing may then be undertaken with the component (rather than polyvalent) antisera by tube agglutination and by biochemical tests

Treatment

Replacement of fluid and attention to electrolyte balance par ticularly potassium deficiency are of paramount importance Published results of antibiotic therapy are conflicting this is not surprising since the precise aetiological agent remains uncertain Combined therapy with oral neomycin and bacitracin is worthy of trial

STAPHYLOCOCCAL ENTERITIS

Diarrhoea of varying severity may complicate the use of any of the oral broad spectrum antibiotics Stool cultures may show the usual intestinal flora or there may be a predominance of yeasts Pseudomonas and Proteus The diarrhoea ceases when the antibiotic is discontinued

Apart from these relatively mild instances there is also a more

severe and often fatal pseudo membranous enterocolitis which may follow these antibiotics especially in the post-operative period or in association with intestinal intubation The stools contain Staph aureus which grows out in pure culture and is found to be resistant to most of the commonly used antibiotics It produces an enterotoxin which leads to both gastro-intestinal and systemic symptoms resembling cholera Copious diarrhoea abdominal distension vomiting fever and sweating make the patient dehydrated collapsed shocked and even mentally confused

If the stool smear reveals Staph aureus the antibiotic should be discontinued and replaced by anti staphylococcal agents such as erythromycin novobiocin vancomycin and oleandomycin to which the organism may still be sensitive Fluid replacement must be adequate

DYSENTERY

BACILLARY DYSENTERY

The *Shigella* group of organisms gain entry to the gastro intestinal tract in contaminated food or water and cause acute inflammation of the large bowel and sometimes also of the lower ileum Abdominal colic and diarrhoea are the principal acute symptoms The stools in severe cases contain mucus pus and blood but a mild illness may be associated with only a few semi formed stools of otherwise normal appearance

The clinical *diagnosis* is confirmed by isolation of the organism from the mucous exudate in fresh faeces Specific serological anti bodies develop during convalescence but they are of no value in the diagnosis of infection They may be of retrospective help during epidemics

Treatment

The sulphonamides tetracyclines chloramphenicol streptomycin and polymyxin are all effective in controlling acute bacillary dysentery due to Shigella organisms Sulphadiazine or a non absorbable sulphonamide is satisfactory as a first choice in a temperate climate but in the dehydrated and possibly oliguric patient in the tropics tetracycline is preferable

Bacteriostatic drugs may relieve the symptoms satisfactorily but relapses occur or organisms continue to be excreted In this small proportion of infections a bactericidal drug such as polymyxin should be administered orally

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hepatic or systemic involvement However it may be toxic even in the recommended daily dose of 65 mg (gr 1) subcutaneously for ten days It should be kept in reserve for relapses or cases which fail to respond to other less toxic drugs It should not be given to patients with cardiovascular disease since it is liable to cause cardiac arrhythmia nor to patients with renal disease because of the risk of accumulation Electrocardiographic records should always be taken in the course of treatment Emetine bismuth iodide (E B I) is effective against cysts but since it is not absorbed its value is restricted to the intestinal disease A course of 0 2 g on each of twelve evenings may provoke nausea although the powder is packed in gelatine capsules It may also cause diarrhoea which is unwelcome in acute amoebic dysentery

Group 2 drugs The pentavalent arsenicals act on both the vegetative forms and cysts Bismuth glycolylarsanilate (milibis) is as effective and less toxic than carbarsone Since they are poorly absorbed a high concentration is maintained in the intestine they are therefore ineffective against extra intestinal lesions The dose of bismuth glycolylarsanilate is 0 5 g thrice daily and of carbarsone 0 25 g thrice daily for seven to ten days

Group 3 drugs The iodoxyquinolines act on both vegetative forms and cysts in the intestine but are not effective against extra intestinal organisms Diiodohydroxyquinoline (diodoquin) is given orally in doses of 30 mg /kg daily for three weeks Iodochlorhydroxyquinoline and chiniofon may also be given by mouth but they have no advantages by this route over diodoquin However unlike the highly insoluble diodoquin they may be used as retention enemas in strengths of 1 per cent iodochlorhydroxyquinoline or 4 per cent chiniofon

Group 4 drugs Chloroquine is so rapidly absorbed in the upper bowel that it does not affect intestinal amoebiasis but it is a valuable tissue amoebicide for hepatitis Each 0 2 g tablet of chloroquine contains 0 15 g of chloroquine base in which form dosage is usually expressed After initial loading doses of 0 6 g (four tablets) of chloroquine base on the first and second days a maintenance dose of 0 3 g (two tablets) may be continued for fourteen to twenty-one days Camoquin in repeated courses of 0 6 g daily for ten days has also proved useful in the treatment of amoebic liver abscess

It has recently been observed that large doses of mepacrine approximating 0 9 g daily for ten days are effective in hepatic amoebiasis

AMOEBIC DYSENTERY

Unlike bacillary dysentery intestinal amoebiasis has a more insidious onset and may pass into a chronic phase in which diarrhoea may be inconspicuous and may even alternate with constipation There may be associated amoebic hepatitis or amoebic abscess of the liver

Because of the insidious onset and persistence of infection intestinal amoebiasis mimics practically every intestinal disorder

Diagnosis

Diagnosis depends upon finding *Entamoeba histolytica* in the mucus of warm fresh stools or in the faeces or biopsy material obtained by sigmoidoscopy It must be distinguished from E coli a non pathogenic inhabitant of the normal human colon E histolytica is the smaller of the two its cysts are also smaller and contain only four nuclei compared with eight in E coli cysts E histolytica is the more active and it is able to ingest red blood corpuscles

If amoebic abscess of the liver is suspected aspiration should be undertaken for the characteristic anchovy sauce contents

Treatment

With a profusion of drugs of proven value available there is danger of over treatment It is therefore necessary to choose the most potent but least toxic combination which will eradicate the infection and minimise the relapse rate There are five groups of drugs in current use

Group 1 Emetine and emetine bismuth iodide
Group 2 Pentavalent arsenicals—the carbarsone compounds and bismuth glycolylarsanilate
Group 3 Iodoxyquinolines—diiodohydroxyquinoline (diodoquin), iodochlorhydroxyquinoline (vioform) chiniofon (yatren)
Group 4 Aminoquinolines—chloroquine and camoquin
Group 5 Sulphonamides antibiotics fumagillin

Group 1 drugs have for long proved their value Emetine hydrochloride attacks amoebae in the intestinal wall and liver with rapid relief of symptoms so speedily in fact that a clinical diagnosis of amoebiasis is often suggested by the results of such a therapeutic trial It arrests growth and migration of the motile amoebae in the tissues and is particularly valuable in active colitis and when there is

nated by carriers leads to intestinal and mesenteric lymph node involvement septicaemia and finally to biliary tract and urinary tract localisation This sequence is accompanied by a clinical picture of fever toxaemia and abdominal symptoms together with evidence of involvement of other organs such as the skin and spleen

The differences between typhoid and paratyphoid fevers are indistinct especially since the clinical picture has been modified by specific chemotherapy

Diagnosis

The clinical suspicion should be confirmed whenever possible by laboratory tests

Isolation of the organism from the blood or bone marrow during the first week of typhoid fever from the faeces during the second week onwards and from the urine during the third and fourth weeks The blood faeces and urine should also be cultured for other salmonellae

Serology During the course of the illness serological agglutinins develop and a significant rise in titre between acute phase and convalescent phase sera strongly suggests recent infection This is the basis of the Widal test in which serial dilutions of sera are titrated against H and O antigens of various salmonellae The development of O antibody in high titre is of greater significance than H antibody which persists for many years after infection or vaccination and shows non specific anamnestic responses to other febrile illnesses In addition the typhoid bacillus possesses a somatic Vi (virulence) antigen to which specific serum antibodies may be demonstrated

If only single convalescent specimens of serum are available and it is impossible to demonstrate a rising titre an O titre of 1 100 or greater is suggestive of active enteric fever whereas a low O with a high H titre only suggests past infection or previous immunisation

Treatment

Chloramphenicol has established itself as the drug of choice in all salmonella infections It should be administered orally for seven to ten days In infants who are unable to tolerate the drug orally it may be given in the form of suppositories which achieve satisfactory serum concentrations

Within three days of treating typhoid fever the toxaemia lessens and the pyrexia subsides thereafter there is continued improvement About two weeks after cessation of treatment there is often a relapse

Group 5 drugs The sulphonamides and antibiotics are not amoebicidal but their value in controlling secondary bacterial infection in the intestine has provided them with a very definite place in the treatment of acute ulcerative amoebic dysentery The sulphonamides or penicillin alone are known to be curative in some instances but the tetracyclines are the most effective Although they provide excellent immediate results there is a significant relapse rate and a direct amoebicide should always be used in combination

Fumagillin isolated from Aspergillus fumigatus has in vitro amoebicidal activity but since it is not antibacterial the intestinal flora is unaltered It has met with mixed success in the intestinal disease and some authorities have ceased to use it It should never be considered as an alternative to the tetracyclines but only as a possible amoebicide to be used in combination with them

Routine for acute dysentery

Oral tetracycline 1 g daily for ten days

Oral diiodohydroxyquinoline 0 65 g thrice daily for twenty one days After the acute dysentery symptoms have subsided oral emetine bismuth iodide 0 2 g each evening for twelve days

If a relapse follows this regime—

Subcutaneous emetine hydrochloride 65 mg (gr 1) daily for ten days

Oral bismuth glycolylarsanilate (milibis) 0 5 g thrice daily for eight days as an alternative to diiodohydroxyquinoline

Oral bacitracin 100 000 units daily for five days with oral neomycin as an alternative to tetracycline

Routine for hepatitis

Oral chloroquine 0 6 g on first and second days 0 3 g sub sequently for fourteen days In addition treat the intestinal infection as above since chloroquine is ineffective against intestinal amoebiasis Emetine hydrochloride camoquin and mepacrine are effective alternative forms of treatment in hepatitis If there is persistent fever after chloroquine the liver should be needled for a possible amoebic abscess which is aspirated

ENTERIC FEVER

This term usually covers typhoid fever caused by *Salmonella typhi* and paratyphoid fever due to *S paratyphi A B and C* Ingestion of the causal organism in infected food or water usually contami

Diagnosis

In the course of an epidemic the clinical picture is characteristic Nevertheless specific laboratory confirmation should be sought at the onset of an epidemic or to detect sporadic infection by (*a*) *isolation of the organism* from mucus in the watery stools or from rectal swabs Smears stained with carbol fuchsin exhibit characteristic forms and the material should also be cultured in peptone water In the course of a few hours a surface pellicle develops this is stained for bacilli (*b*) *Slide agglutination* of suggestive colonies using specific antiserum may also be an aid to identification

Treatment

The cholera vibrio is sensitive to the sulphonamides tetracyclines chloramphenicol streptomycin neomycin and polymyxin and any of these agents eliminates organisms from the stools However they do not neutralise the toxaemia nor of course correct the severe and often fatal electrolyte imbalance antibiotics are of only secondary therapeutic importance to replacement therapy with salt and water Sulphonamides in fact may prove dangerous to the oliguric patient who should be managed along the lines laid down for acute renal tubular necrosis

INTESTINAL TUBERCULOSIS

Intestinal tract tuberculosis may follow the repeated ingestion of large numbers of virulent organisms in the susceptible individual The infecting doses may be conveyed in the swallowed sputum of patients with pulmonary disease or in infected milk Early detection and treatment of pulmonary tuberculosis pasteurisation of milk and improved living standards have all contributed to the decline in incidence

Common sites of involvement are the terminal ileum and caecum or the peri anal region Ulceration leads to caseation sinuses or internal fistulae and an attempt at healing leads to fibrosis strictures and distortion Symptoms may be due to either or more frequently a combination of these features The patient complains of intermittent and later continuous diarrhoea with recurrent attacks of small intestinal colic and discomfort in the right lower quadrant Tenderness and a palpable mass may be found over the caecum A tuberculous ischio-rectal abscess may lead to fistula in ano

with return of fever and positive blood and stool cultures Chloramphenicol is bacteriostatic rather than bactericidal, and this together with the patient s lack of resistance may account for the recrudescence It is certainly not due to the development of chloramphenicol resistant typhoid bacilli for a good response follows further chemotherapy The relapse rate is sufficiently common to recommend a routine five day course of chloramphenicol two weeks after the end of the first course

When cortisone is given in addition to chloramphenicol the period of toxaemia and pyrexia is shortened This combined regime *has no untoward sequelae and should be considered in seriously ill* patients in whom early control of fever and toxaemia is urgent

Antibiotic therapy has not appreciably reduced the incidence of perforation or haemorrhage of the typhoid ulcer which may occur *during early convalescence when the patient is afebrile and symptom* free Chemotherapeutic control should not therefore be an excuse for premature overactivity

Chloramphenicol has proved disappointing in the control of typhoid carriers who should remain under close supervision They may respond to large doses of a bactericidal antibiotic such as penicillin However if the faeces continue to show the organism while the urine is sterile the gall bladder is the likely seat of infection and cholecystectomy must be considered This is an effective means of ending the carrier state

Apart from the supervision of carriers prevention of typhoid fever lies in maintaining safe sanitation and a high standard of hygiene together with an intensive programme of active immunisation The vaccine in common use contains *heat killed typhoid and* paratyphoid organisms Three weekly subcutaneous or intracutaneous inoculations should be followed by a booster dose every three years or whenever undue exposure by overseas travel or an epidemic demands it

CHOLERA

Cholera is acquired by the ingestion of food and water contaminated by vibrio-infested faeces Flies help to spread the infection *Vibrio cholerae* liberates an irritating endotoxin in the intestine producing an acute enteritis with severe diarrhoea and vomiting The fluid and electrolyte loss is so great that the patient becomes severely dehydrated shocked and collapsed oliguric and eventually anuric

Treatment

Intravenous sodium antimony tartrate is the treatment of choice commencing with 0 3 g and increasing daily by 0 3 g to a total dose of 2 g Complicating portal hypertension may in certain instances demand surgery

OTHER FLUKES

Paragonimus westermani is found in the Far East and parts of Africa and South America It causes pulmonary symptoms due to lodgment of migrating larvae The characteristic eggs are found in the sputum and faeces

Clonorchis sinensis and *Fasciola hepatica* are found in the Far East The fluke invades the liver causing cirrhosis, and the bile passages causing suppurative cholangitis

Fasciolopsis buski is found in the Far East Burma and India The worms lodge in the duodenum and jejunum causing symptoms similar to a peptic ulcer or a picture of high intestinal obstruction There may be diarrhoea with much toxaemia and malnutrition Diagnosis is confirmed by finding the appropriate eggs in the faeces or duodenal juice

Treatment

Paragonimus and hepatic fluke infections are difficult to treat Oral chloroquine in a dose of 5 mg base/kg daily should be given for periods of several weeks Fasciolopsis buski is removed by treatment with oral hexylresorcinol It is given in a hard gelatine capsule to avoid buccal ulceration An adult dose of 1 g is taken on an empty stomach and followed by a saline purge This treatment may be repeated one week later to achieve maximum worm expulsion

CESTODES OR TAPE WORMS

These worms cause a variety of infections in Great Britain Northern Europe and many other parts of the world

TAENIA SAGINATA AND TAENIA SOLIUM

T saginata is contracted by eating undercooked beef whereas *T solium* infection follows the ingestion of undercooked pork

The patient presents with abdominal discomfort and diarrhoea or more commonly because he has seen segments of worm in the stool The larvae of T solium may migrate to the brain causing cerebral

Diagnosis

A chest radiograph should be routine in all patients with chronic diarrhoea or peri anal inflammation Tubercle bacilli may be found in a discharging sinus, in the faeces, or in biopsy material obtained at operation A positive intradermal tuberculin test at very high dilution is in favour of tuberculosis whereas a negative result is more suggestive of Crohn s disease which may present clinical and histological confusion

Treatment

Specific anti tuberculous chemotherapy is continued for one year and special attention is paid to diet which should be bland nutritious and of low residue Surgical procedures may be necessary for quiescent lesions causing mainly mechanical symptoms

HELMINTH INFECTIONS

The common human helminth infestations are due to trematodes cestodes or nematodes (p 63 and Table 20)

TREMATODES OR FLUKES

SCHISTOSOMIASIS

S haematobium originated in the Nile valley and is now endemic in Africa and Asia It causes vesical polyposis with haematuria and also pulmonary fibrosis with pulmonary hypertension *S mansoni* has an extensive distribution in Egypt Africa the West Indies and Central and South America and *S japonicum* is encountered particularly in the Far East These latter two flukes cause dysentery peri rectal abscess and hepatosplenomegaly with portal hyper tension

Diagnosis

The eggs of S haematobium are found in the urinary sediment Cystoscopy may show a polypoid lesion and biopsy is useful to demonstrate the ova

The eggs of S mansoni and S japonicum are found in the faeces Proctoscopy reveals granulomatous nodules in the rectum and scrapings or biopsy may show the eggs Liver biopsy may reveal granulomata containing fragments of ova

Trichini is	Trichinella spiral s	Pork-eating countries	Vomiting di rrhoea Myalgia Urticaria	Skin test Complement fixation test Muscle biopsy	Corticosteroids for allergic manifestations
Ascarias s	Ascaris lumbr coides	World wide	Intestinal col c Bil ry obstruction Pulmonary infiltration	Eggs in faeces	Hexylresorcinol or piperazine citrate
Filariasis	Wuchereria bancrofti Wucherer a malayi	Various endemic zones throughout the tropics	Elephantiasis	Microfilariae in blood smears	Diethylcarbamazine
Loiasis	Loa loa		Calabar Swelling		
Onchocerciasis	Onchoce ca volvulus		Blindness Pruritus	Biopsy	*Suramin*
Dracontiasis	Dracuncul s medinensis		Visible subcutaneous worm		Remove worm by coiling around stick
Ancylostomiasis	(Hookworm) Ancylostoma duodenale Necator americanus	Humid tropics Mediterranean Asia N and S America	Ground itch Alternating diarrhoea constipation Anaemia lassitude	Eggs in faeces	Tetrachlorethylene Iron
Trichuriasis	(Whipworm) Trichuris trichiura	World wide	Abdominal symptoms Urticaria	Eggs in faeces	Tetrachlorethylene hexylresorcinol or oil of chenopodium
Strongyloidiasis	Strongyloides stercoral s	As for hookworm	Epigastric pain Diarrhoea Urticaria Pulmonary symptoms	Larvae in faeces or duodenal drainage	No effective anthelmintic Try gentian violet Corticosteroids for allergic manifestations

TABLE 20 — DIAGNOSIS AND TREATMENT OF HELMINTH INFECTIONS

Infection	Causal helminth	Geographical distribution	Clinical features	Diagnosis	Treatment
Schistosomiasis	S haematobium S mansoni S japonicum	Africa Asia W Indies S America Africa Asia	Vesical polyposis haematuria Dysentery Peri rectal abscess Hepatosplenomegaly Portal hypertension	Eggs in urine Cystoscopy Proctoscopy Eggs in faeces Liver biopsy	Sodium antimony tartrate
Pulmonary distomiasis	Paragonimus westermani	Asia Africa S America W Indies	Pulmonary symptoms	Eggs in sputum and faeces	Chloroquine
Hepatic distomiasis	Fasciola hepatica Clonorchis sinensis	World wide Asia	Hepatic cirrhosis Cholangitis	Eggs in faeces duodenal or biliary drainage	Chloroquine
Intestinal distomiasis	Fasciolopsis buski	Asia	Similar to peptic ulcer or upper intestinal obstruction Diarrhoea	Eggs in faeces	Hexylresorcinol
Taeniasis	T saginata T solium Diphyllobothrium latum	World wide	Various intestinal symptoms	Segments in faeces	*Mepacrine or dichlorophen* Vitamin B_{12}
Hydatid disease	Echinococcus granulosus	World wide	Depending on site commonly hepatic Allergic symptoms due to cyst rupture	Calcified cysts by radiography Complement fixation test Casoni t st	Surgical removal Corticosteroids for allergic man festations
Oxyuriasis	(Threadworm) Oxyuris vermicularis	World wide	Pruritus ani	Eggs in f eces	P perazin c tr t

THREADWORMS

Threadworm infestation is the commonest helminth infection in Great Britain It is commoner in children who are well disposed to perpetuate the anus to mouth cycle of infection The most usual symptom is pruritus ani which may be sufficiently troublesome to cause insomnia

The *diagnosis* is readily made by finding the eggs in specimens of faeces or on anal swabs It is advisable to examine all members of a household when infestation has been revealed in one member

Treatment

Oral piperazine citrate 50 mg /kg daily in divided doses and continued for seven days is highly effective against human thread worms

TRICHINIASIS

Trichiniasis due to *Trichinella spiralis* may cause diarrhoea and vomiting one to four days after ingestion followed by myalgia and urticaria during its migration elsewhere in the body

Diagnosis may be confirmed by a skin test (Table 24) by a specific complement fixation test or by identification of the encysted larvae in a muscle biopsy

Treatment There is no specific chemotherapy but alarming allergic manifestations may be controlled by the prompt use of corticosteroid therapy

ASCARIASIS

Ascariasis due to *Ascaris lumbricoides* may present with intestinal colic or biliary obstruction or rarely a picture of bronchial asthma or pulmonary infiltration during its stage of pulmonary migration Diagnosis is confirmed by recovery of eggs in the faeces

Treatment Hexylresorcinol may be given in a dose of 1 g to the fasting adult and followed by a saline purge If hookworm is also present it is advisable to give an adult dose of 1 ml oil of cheno podium combined with 2 ml of tetrachlorethylene on an empty stomach followed in two hours by a saline purge For children piperazine citrate may be given in a single dose of 75 mg /kg or alternatively diethylcarbamazine (10 mg /kg) daily for ten days in divided doses

cysticercosis and focal epilepsy, or they may lodge in muscles with consequent aching of the limbs

Diagnosis

This depends on recovery of segments from the faeces Cysts of T solium in brain or muscle eventually calcify and may be shown in radiographs of chest skull or limbs

Treatment

Intestinal tapeworms are best treated in hospital by a regime of starvation purging and one of the anthelmintic drugs Mepacrine is not lethal to the tapeworm but dislodges the grip of the scolex hooks and suckers on the intestinal wall It is best given in a dose of 1 g by duodenal tube after two days starvation and followed twenty minutes later by 1 2 fluid oz of magnesium sulphate By contrast dichlorophen exerts a direct destructive action on the helminth when given in a dose of 70 mg /kg body weight It is given in the morning on an empty stomach because it has a purgative action no other preliminary preparation is necessary The segmented bodies are easily recognised in the faeces after mepacrine but not after dichlorophen which expels the tapeworm as a disintegrated jelly

The traditional filix mas (6 to 9 ml) is by comparison an inferior form of therapy

Diphyllobothrium latum is contracted by eating raw fresh water fish it is prevalent in Northern Europe Diarrhoea and general toxaemia are associated with a macrocytic anaemia due to diversion of vitamin B_1 from the host

Diagnosis depends on the recovery of the eggs from faeces

Treatment is as for T solium and T saginatum but vitamin B_{12} is also needed to correct the macrocytic anaemia

Taenia echinococcus (Echinococcus granulosus) causes hydatid disease This is discussed more appropriately with hepatic infections (p 185)

NEMATODES OR ROUNDWORMS

Roundworm infection is common in tropical and subtropical climates those which occur particularly in Great Britain are infections with *Oxyuris vermicularis (threadworm) Trichinella spiralis* and *Ascaris lumbricoides* Others often seen in the tropics are due to *filaria Dracunculus hookworm Trichuris trichiura (whipworm)* and *Strongyloides stercoralis*

but more toxic are oil of chenopodium and hexylresorcinol Iron is given for the anaemia

TRICHURIASIS

Trichuriasis due to *Trichuris trichiura* (*whipworm*) has a world wide distribution The patient may be symptom free or may suffer nervousness urticaria with eosinophilia or abdominal symptoms Diagnosis is made by finding the eggs in the faeces

Treatment

There is no satisfactory anthelmintic treatment and repeated courses of tetrachlorethylene hexylresorcinol oil of chenopodium or emetine hydrochloride are necessary

STRONGYLOIDIASIS

Strongyloidiasis due to *Strongyloides stercoralis* is prevalent in the humid tropics It causes epigastric discomfort and general toxic symptoms Bronchial migration may be associated with respiratory symptoms There is a constant eosinophilia

Diagnosis is made by finding larvae in duodenal drainage fluid stools or occasionally in the sputum

Treatment

There is no effective anthelmintic gentian violet is usually recom mended in adult doses of 65 mg thrice daily for two weeks When there is obvious pulmonary involvement it should be given intra venously as a 0 5 per cent solution in a dose of 20 ml every other day for one week Antihistamine or corticosteroid therapy is given to control allergic manifestations of the disease

FILARIASIS

There are various endemic zones throughout the tropics for the several different filarial worms

Wuchereria bancrofti and *W malayi* enter the lymphatic system causing lymphangitis and lymphadenitis, and a fibrous tissue reaction eventually leads to elephantiasis Microfilariae are found in the peripheral blood at night but return to the splanchnic circulation when the patient is active by day

Loa loa causes Calabar swellings which appear as transient areas of oedema and induration on the arms

Onchocerca volvulus migrates through the skin and subcutaneous tissues causing itching eruptions or it may involve the tissues of the eye producing conjunctivitis and later loss of vision

Dracunculus medinensis has an easily visible subcutaneous track, which is often secondarily infected with pyococci Attacks of urticaria may occur as these worms migrate through the body

Treatment

Infection with W bancrofti W malayi and loa loa are treated with diethylcarbamazine commencing with 50 mg thrice daily and gradually increasing over a week to 0 2 g thrice daily for a further two weeks

When the causative nematode is Onchocerca volvulus 1 g intravenous suramin is given weekly for five weeks

The traditional treatment of Dracunculus medinensis is to pull out the subcutaneous worm by coiling it around a stick at the rate of 1 cm daily making certain that it does not break off during the manipulation Its speed of removal may be increased by injecting along the track an emulsion containing phenothiazine olive oil and procaine which relax the worm and enable it to be removed intact

ANCYLOSTOMIASIS

Ancylostomiasis or hookworm disease is caused by infection with *Ancylostoma duodenale* or *Necator americanus* The larvae penetrating the skin cause ground itch and the adult intestinal worm may lead to abdominal symptoms including alternating diarrhoea and constipation as well as lassitude and anaemia

Treatment

Tetrachlorethylene in a dose of 2 ml is given on an empty stomach and followed by a saline purge in two hours Also effective

or splenic aspiration enables the Leishman Donovan bodies of kala azar to be identified in the cellular accumulations

Malaria affects the liver both by exciting a histiocytic reaction and by the effects of the associated fever and malnutrition on the liver cells Malarial pigment is present in the Kupffer cells There are no clinical features specific for the liver The cellular reaction with increased serum globulin values is responsible for positive seroflocculation tests which do not indicate liver cell damage in this disease

Toxoplasmosis is associated with focal non specific changes in liver cells The infantile form probably acquired in utero from inapparent maternal infection may present as neonatal jaundice and hepatomegaly The jaundice is due to direct hepatic involvement and to haemolysis

Amoebiasis is considered on page 170

METAZOAN INFECTIONS

Schistosomiasis S mansoni and S japonica deposit eggs in the portal zones of the liver These excite a fibrous tissue reaction with consequent portal hypertension (p 176)

Fasciola hepatica and *Clororchis sinensis* affect the liver and may cause hepatic cirrhosis (p 177)

Hydatid disease is due to T echinococcus Man is infected by contact with the excreta of dogs who have been infected by sheep Ingested ova burrow through the intestine into portal radicles and so reach the liver where they develop into multilocular hydatid cysts

The disease is endemic in sheep raising countries where dogs have access to infected offal It is rare in Great Britain apart from some areas of Wales The uncomplicated cyst may be silent Complications include secondary infection and rupture into intestines peritoneum bile ducts veins or through the diaphragm

Diagnosis is confirmed by the Casoni test (Table 24) Antigen is prepared from the sterile fluid of an hydatid cyst rich in scolices and hooklets and it is injected in a dose of 0 2 ml intradermally A positive reaction consists of a wheal and surrounding erythema within thirty minutes This is an immediate type or histamine type response This response indicates that the patient has been infected with hydatid disease and at some time the hydatid cyst has leaked A negative reaction does not exclude the disease but suggests that

CHAPTER 16

LIVER, BILIARY TRACT AND PANCREAS

THE LIVER

THE liver is frequently involved in general infections This may be due to bacterial toxins, to direct bacterial invasion or to the secondary effects of anoxaemia anaemia or malnutrition The infective agent reaches the liver via the portal vein (pylephlebitis) via the bile ducts (cholangitis), via the hepatic artery (septicaemia) or directly by trauma Pathologically the liver shows a generalised reticulo-endothelial reaction sometimes with granulomatous formation The liver cells may show focal necrosis and fatty or other degenerative changes The hepatic involvement is often but an incident of the generalised infection under these circumstances it may not be recognised clinically nor does it demand special treatment other than that which is described elsewhere for the generalised disease Conversely haemolysis accompanying certain infections may cause jaundice simulating primary liver disease

FUNGAL INFECTIONS

Actinomycosis

Hepatic involvement is secondary to intestinal disease especially of the caecum or appendix The liver contains multiloculated thick walled abscesses which extend to adjacent parts and to the abdominal wall forming sinuses The patient is toxic febrile, wasted and anaemic with an enlarged tender and irregular liver

Diagnosis is confirmed by finding Actinomyces israeli in aspirated pus or in histological sections from sinus tracts or liver tissue

Hepatic involvement is an incident in *disseminated coccidioidomycosis* and *histoplasmosis* The hepatic lesions are granulomatous and may be demonstrated by aspiration liver biopsy The biopsy should be cultured on Sabouraud s medium

Small abscesses of the liver may occur in *moniliasis* and *aspergillosis* but they are either silent or incidental to an overwhelming generalised infection

PROTOZOAL INFECTIONS

Leishmaniasis is essentially a reticulo-endothelial disease causing a widespread histiocytic reaction in the liver Aspiration liver biopsy

Infection may reach the liver via the portal vein from intra abdominal infections In the new born septic phlebiti of the umbilical vein may spread to the liver Rarely multiple liver abscesses complicate a systemic pyaemia or a solitary abscess follows a penetrating wound or direct spread from an adjacent septic focus Amoebic abscesses may become secondarily infected Approximately one half of all hepatic abscesses have no known predisposing cause Infecting organisms include streptococci staphylococci and the Gram negative enteric bacilli mixed infections are common

The patient appears toxic and wasted with spiking fever There is dull pain over the enlarged tender liver Jaundice is rare and late A polymorphonuclear leucocytosis is constant The offending organism may be identified by blood culture Aspiration of the liver with culture of part of the material obtained may be diagnostic Fluoroscopy may show a high immobile right diaphragm

Treatment consists whenever possible in drainage of the abscess and local instillation of the appropriate antibiotic in addition to its systemic administration

Tuberculosis

Although the liver is frequently involved by haematogenous spread it is inimical to the growth of the tubercle bacillus and lesions tend to heal spontaneously Hepatic tuberculosis is therefore seldom of clinical importance

Disseminated tuberculosis may result in miliary hepatic granuloma formation Tuberculomata and tuberculous pyelephlebitis may rarely follow rupture of caseous material into the portal vein from lymph nodes Clinical features are usually due to the concomitant active tuberculosis elsewhere Aspiration liver biopsy may reveal miliary granulomata sections should be stained for tubercle bacilli and an unfixed portion of the biopsy cultured and injected into a guinea pig

Brucellosis

Miliary granulomata due to brucellosis may be widespread in the liver even in the absence of clinical manifestations of hepatic involvement Aspiration biopsy may therefore be useful in diagnosis but care is necessary in their interpretation for hepatic granulomata are not specific to brucellosis A small portion of the unfixed biopsy specimen should be cultured although results are often negative

a cyst, if present, has not leaked to sufficient degree to sensitise the patient

Complement fixing antibodies against an antigen prepared from fresh hydatid fluid are present in 75 per cent of patients harbouring living cysts

The cyst wall may calcify and be demonstrated radiologically Exploratory aspiration must be condemned as causing widespread peritoneal dissemination or fatal anaphylaxis

Prevention consists in control of canine infection There is no medical *treatment* and surgical removal must always be considered for the risk of rupture is great Alarming allergic manifestations may demand corticosteroid therapy

SPIROCHAETAL INFECTIONS

Syphilis

The liver is involved in all stages of syphilitic infection but symptoms and signs suggesting hepatic disease are very rare The liver is teeming with spirochaetes in congenital syphilis diffuse hepatitis being followed by peri cellular fibrosis During the course of secondary syphilis the liver contains miliary granulomata The essential hepatic lesion of tertiary syphilis is the gumma It consists of a caseous mass circumscribed by fibrous tissue and distorting the shape of the liver (hepar lobatum) This is a local rather than a diffuse lesion a true cirrhosis does not follow tertiary syphilis

Aspiration liver biopsy may be useful in diagnosis but it is rarely necessary

Weil s disease

Jaundice is a prominent feature of Weil s disease developing between the fourth and seventh day in three quarters of patients It is a grave sign for the disease is rarely fatal in the absence of icterus The liver shows only scattered local necroses with con spicuous mito es these changes do not parallel the degree of jaundice

BACTERIAL INFECTIONS

Pyogenic liver abscess

The present infrequency of liver abscesses is largely due to successful control of infections by specific chemotherapy and to early diagnosis of the common antecedent acute appendicitis

The total serum bilirubin concentration confirms the clinical impression of icterus Deep jaundice implies marked liver cell destruction and a prolonged clinical course The serum alkaline phosphatase level is slightly raised but not above 30 King Armstrong units per 100 ml an arbitrary dividing line between hepatocellular and obstructive jaundice The differential serum protein levels are of little practical diagnostic value because they are unchanged in the average case The zinc sulphate test is positive early and the thymol turbidity later in the disease

Treatment

There is no specific chemotherapy against the small resistant hepatitis virus Uneventful recovery is usual if the patient is kept in bed while acute symptoms persist Diet is low in fat only while nausea persists and then the patient may eat anything he wishes If adequate supervision is possible the patient may be allowed up although jaundice is still present so long as he rests in bed for one hour after each meal A convalescent holiday is permitted when the liver is no longer tender excess urobilinogen has disappeared from the urine and the serum bilirubin level is less than 1 5 mg /100 ml

The development of neuropsychiatric changes or frank hepatic coma demands more active treatment Products of bacterial action on protein in the intestine are believed of importance in its aetiology so dietary protein is stopped a purge and enema given and neomycin (6 g daily by mouth) administered Prednisolone may be of value in the control of toxaemia due to fulminant hepatitis

Prevention is made difficult by lack of recognition of virus carriers the numerous available methods of transmission and the resistance of the hepatitis viruses to destruction Infective hepatitis control lies in perfect sanitation Ideally hospital patients should be barrier nursed with the same strict routine adopted for poliomyelitis or enteric fever patients Those treated at home need not be segregated from other close members of the family who can be assumed to have suffered maximal exposure during the pre icteric period

Infective hepatitis may be prevented by the intramuscular injection of normal human serum gamma globulin in the dose of 0 02 ml per kg of body weight if given after exposure and up to six days before the onset of symptoms This method is applicable to schools institutions and camps where an epidemic starts and a large population is at risk Gamma globulin injections do not protect against

Tularaemia

Dissemination of Past tularensis involves the liver with the formation of granulomata Clinical manifestations of hepatic involvement are rare

VIRUS INFECTIONS

VIRUS HEPATITIS

The essential lesion is an acute inflammation of the entire liver The clinical picture varies widely ranging from slight malaise with no obvious jaundice to the severe fulminant variety culminating in hepatic coma There are no clinical nor pathological differences between serum and infective hepatitis the distinction is based on the history of contact or injections or on a study of the mode of spread in any epidemic *The incubation period of infective hepatitis is* fifteen to forty days and of serum hepatitis sixty to one hundred and sixty days Patients with serum hepatitis tend to have a more severe illness because it is an added strain to the initial malady for which they are receiving injections or transfusions

Acute icteric hepatitis is the commonly recognised clinical form of the disease In most patients there is a pre icteric stage lasting three or four days corresponding with a period of viraemia Loss of appetite may be accompanied by loss of desire to smoke or drink alcohol malaise nausea vomiting and abdominal distension Fever of 100° to 103°F occurs in about half the patients lasting two to five days and subsiding with the appearance of the jaundice The liver enlarges towards the end of the prodromal period and the edge is usually tender The icteric stage is preceded by darkening of the urine pallor of the stools and sometimes severe diarrhoea which is followed by constipation Pruritus may be experienced with the onset of jaundice but rarely persists for longer than one week

Diagnosis

There is no specific diagnostic test The earliest detectable abnormality occurring in the pre icteric phase is the presence of bilirubin in the urine This permits a confident clinical diagnosis to be made before jaundice is obvious *Every stool should be inspected* and the colour recorded The onset of jaundice is marked by lightening of the stool colour but rarely to the extent seen in obstructive lesions of the extra hepatic bile passages Reappearance of pigment in the stools denotes impending recovery

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cycline is however of value in preventing septic complications which may otherwise progress to empyema of the gallbladder

PANCREAS

Bacterial infections

Pancreatitis is commonly an autolytic non infective process secondary to obstructive disease of the pancreatic duct or biliary system or due to direct penetration by adjacent disease of stomach or duodenum It is commoner in alcoholic patients with hepatic cirrhosis Bacteria may invade the necrotic autolysed pancreatic tissue the offending organisms being usually derived from the intestinal tract This complication may be minimised by treatment with a bactericidal drug such as streptomycin which is effective against these Gram negative organisms It is given by intramuscular injection in doses of 1 g eight hourly for five days and may be combined with an oral sulphonamide for a similar period

Virus infections

Acute pancreatitis is a well recognised complication of mumps and less often of infective hepatitis It may possibly accompany Coxsackie virus infections It is suggested by severe upper abdominal pain which radiates to the back and is accompanied by repeated vomiting It is accompanied by a steep rise in the serum amylase level There is no specific chemotherapy and attention is directed to symptomatic measures and correction of fluid balance The disease is self limiting and pancreatic function eventually returns to normal

serum hepatitis The avoidance of blood products or unsterile parenteral inoculations remains the chief method of control of serum hepatitis Chemical disinfectants are useless and sterilisation is best performed by dry heat or steam or by boiling for at least ten minutes

Yellow Fever is discussed on page 130 and *Infectious mononucleosis* on page 129

BILIARY TRACT

Acute cholangitis

Acute infections of the biliary tract are usually due to the ascent of intestinal organisms in the presence of partial or total biliary obstruction The most frequent accompaniment is a gallstone in the common bile duct but cholangitis also complicates traumatic stricture of the bile duct and occasionally occurs above a malignant obstruction

The bile becomes thick and turbid the common bile duct is thickened and dilated and the liver shows changes varying from mild portal zone inflammation to frank abscess formation The infection is usually due to Gram negative intestinal organisms

Exacerbations of the cholangitis follow mucosal swelling and inflammation with complete obstruction to bile outflow The temperature rises often with a rigor jaundice deepens with bilirubinuria and pale stools and there is right upper quadrant abdominal discomfort and transient pruritus (*Charcot s intermittent biliary fever*) During this period blood and aspiration liver biopsy material may be positive on culture Plain X ray of the abdomen may show gallstones in the gallbladder or common bile duct

Treatment Antibiotics are only temporarily effective in controlling the cholangitis if the bile duct remains obstructed A wide spectrum antibiotic such as tetracycline is given in full dosage and the obstruction relieved at the appropriate moment

Acute cholecystitis

The primary event is obstruction of the cystic duct by a gallstone The imprisoned bile has a toxic effect on the gallbladder wall which becomes necrotic and susceptible to secondary bacterial invasion usually with Esch coli and various streptococci

Treatment In the early stages acute cholecystitis is a chemical inflammation so chemotherapeutic agents are ineffective Tetra

of a structural urinary tract abnormality persistence of the same organisms in successive specimens the demonstration of pus and blood in the urine or an association with debilitating diseases or in females with gynaecological disorders

7 Abacterial pyuria should not be attributed to a rare fungal protozoal or viral cause until a tuberculous lesion has been excluded by careful bacteriological and radiological investigations

TREATMENT (Table 21)

A citrate mixture is used to relieve symptoms and to render the urine alkaline An alkaline urine also facilitates the action of streptomycin and tends to lessen the risk of sulphonamide crystalluria

An oral absorbable sulphonamide is sufficient to cure uncomplicated infections due to *Esch coli* or most strains of *Aerobacter aerogenes* A mixed infection may demand the use of tetracycline or a combination of streptomycin with a sulphonamide

Proteus infections tend to be persistent and difficult to eradicate with antibiotics Strains vary in their susceptibility to different antibiotics so it is usually a matter of trial with those shown to be most promising by in vitro testing This may include tetracycline chloramphenicol or a combination of streptomycin with a sulphonamide Some strains are reported as moderately sensitive to novobiocin particularly in an acid urine

Pseudomonas infections demand polymyxin since it is clearly the most effective antibiotic This agent is also effective against Esch coli and Aerobacter infections so it is a useful drug for the treatment of mixed infections

Infection due to *Str faecalis* responds to large doses of penicillin This may also be effective against staphylococcal infections but urinary tract infections are often due to an antibiotic resistant hospital strain of Staph aureus The drug *in least current use in that hospital* is the most effective anti staphylococcal agent at any given time If tetracycline is ineffective it is necessary to be guided by the results of antibiotic sensitivity tests these may dictate the use of erythromycin novobiocin or vancomycin in combination

CHRONIC URINARY TRACT INFECTIONS

Chronic urinary tract infections are far less amenable to treatment and demand investigations for congenital abnormalities calculi hydronephrosis diverticula of the bladder prostatic hypertrophy and

CHAPTER 17

URINARY TRACT

URINARY tract infections are liable to develop insidiously to recur and to be followed by chronic pyelonephritis Early detection and treatment may prevent the later development of chronic renal disease General principles include

1 Each episode must be regarded as acute pyelonephritis even if the clinical picture is only that of cystitis associated renal involvement cannot be excluded
2 Infection is liable to follow catheterisation When this procedure is essential it should be performed under stringent aseptic conditions
3 Underlying anatomical abnormalities in the urinary tract must be sought and when possible corrected Chemotherapy is only temporarily effective in the presence of such abnormalities Intravenous pyelography should be routinely performed in all patients hospitalised with urinary tract infections cystoscopy and retrograde pyelography must also be considered
4 The infecting organism should be isolated and its antibiotic sensitivity determined as soon as possible The first morning specimen is preferable to random samples because the stagnant overnight urine in the bladder has been allowed the longest incubation time The most commonly found pathogen is *Esch coli* followed in frequency by *Str faecalis Proteus Aerobacter aerogenes Ps pyocyanea* and *Staph aureus* Whereas Esch coli usually appears alone in an acute uncomplicated infection mixed infections predominate when there are structural abnormalities of the urinary tract or after repeated catheterisations
5 Inability to isolate an organism may be due to the presence of a bacteriostatic agent in the urine A sterile specimen of urine obtained immediately on completion of treatment cannot be regarded as proof of cure Further samples must be examined several days after cessation of chemotherapy
6 Symptomless bacilluria may be due to contamination of the specimen or to low grade or chronic infection A true infection is suggested by a history of previous instrumentation the presence

gynaecological or neurological disorders If these anomalies cannot be corrected chemotherapeutic control is doomed to failure

Tuberculosis of the urinary tract may be masked by secondary infection with other bacteria so investigation of chronic or recurrent urinary tract infections should include repeated examination of early morning specimens of urine for tubercle bacilli by culture and guinea pig inoculation If tuberculosis is detected the principles of treatment are similar to those employed in other systems namely bed rest streptomycin and isoniazid and if feasible surgical eradication under chemotherapeutic cover

Nitrofurantoin (*furadantin*) is a synthetic antibacterial agent which may prove useful in chronic urinary tract infections due to *Proteus* and *Aerobacter* or other organisms which have not responded to sulphonamides or tetracycline It is given by mouth in doses of 5 to 10 mg /kg daily in four divided doses with food for ten days It is contraindicated in the presence of oliguria or severe renal damage

TABLE 21.—URINARY TRACT INFECTIONS: CAUSAL ORGANISMS AND SENSITIVITIES TO CHEMOTHERAPEUTIC AGENTS

Organism	Sulphonamides	Penicillin	Streptomycin	Tetracycline	Chloramphenicol	Polymyxin	Drugs of choice
Escherichia coli	+	−	+	+	+	+	1 Sulphonamide 2 Tetracycline
Aerobacter aerogenes	+	−	±	+	±	+	1 Sulphonamide 2 Tetracycline
Proteus	±	−	±	±	±	−	1 Streptomycin and sulphonamide 2 Novobiocin 3 Tetracycline or chloramphenicol
Pseudomonas pyocyanea	±	−	±	±	−	+	Polymyxin
Streptococcus faecalis	±	+	±	±	+	−	Large doses of penicillin
Staphylococcus aureus	±	±	+	+	+	−	1 Tetracycline 2 Erythromycin, novobiocin, oleandomycin or vancomycin
Mycobacterium tuberculosis	−	−	+	−	−	−	Streptomycin with isoniazid and/or P A S

+Drug usually effective ±Drug sometimes effective −Drug ineffective

TABLE 22.—KNOWN CAUSES OF VIRUS CONJUNCTIVITIS

Causal virus	Clinical findings	Virus isolated from	Serological tests	Treatment
Herpes simplex	Keratoconjunctivitis Dendritic ulcer Involvement of mucocutaneous junctions or C N S	Vesicle fluid Saliva Blood Faeces C S F	Complement fixation Neutralising antibodies	Antibiotics for secondary bacterial infection Cautious radiotherapy
Herpes zoster	Keratoconjunctivitis Uveitis Corneal anaesthesia Vesicles in fifth cranial nerve segment	Vesicle fluid		Antibiotics for secondary bacterial infection Local hydrocortisone Tarsorrhaphy
Adenovirus	Epidemic keratoconjunctivitis Tender pre auricular lymph *nodes*	Scrapings of conjunctiva or cornea	Complement fixation Neutralising antibodies	
Trachoma	Follicular hypertrophy of conjunctiva Pannus formation→corneal scarring	Conjunctiva of upper eyelid	Complement fixation	Tetracycline or chloramphenicol
Inclusion conjunctivitis	Commonly neonatal Pannus formation and corneal scarring *not* a feature	Conjunctiva of lower eyelid	Complement fixation	Tetracycline or chloramphenicol

CHAPTER 18

EYE

BLEPHARITIS

Acute infections of the eyelids are due to various pyogenic cocci and are often associated with purulent conjunctivitis The same organisms cause chronic blepharitis in which a more protracted course is due to the balance struck between the pathogenicity of the organism and the host defences Infection of the eyelids may be localised to abscess of the lash follicle (stye) or of the Meibomian gland (chalazion) Non infective factors contributing to the persistence of blepharitis include the irritation of dust wind and smog

CONJUNCTIVITIS

Classification should be an aetiological one into bacterial viral and parasitic types The old division into purulent mucopurulent and catarrhal varieties depending on the nature of the discharge, is merely descriptive and therefore less satisfactory Purulent conjunctivitis is more likely to be due to a pus producing coccus than to a virus but mixed infection due to both bacteria and virus cannot be classified by the nature of the exudate

Bacterial conjunctivitis is due to a variety of Gram positive cocci or Gram negative bacilli The latter include two members of the Haemophilus group the Koch Weeks bacillus and Moraxella lacunata which are said to cause epidemic conjunctivitis It seems probable that these bacilli may play some synergistic role with a virus in producing highly contagious epidemics of conjunctivitis Ophthalmia neonatorum may be due to any pathogenic bacteria which can be transferred from the maternal birth canal, Staph aureus is now a more frequent cause than N gonorrhoeae and unidentified cervico-vaginal viruses may also play a significant but hitherto ill defined synergistic role with bacteria in its causation

Virus conjunctivitis may occur as an incident of a generalised viraemia as in measles or smallpox when there should be no difficulty in diagnosis Alternatively it may present solely as an infection of the conjunctiva and cornea Keratoconjunctivitis with similar clinical findings may be due to one of several different viruses some of which are recognised (Table 22) and others which have not yet been identified

tubercle bacillus and *Brucella* species these are all rare causes of uveitis *Toxoplasma* infection is being increasingly recognised as a cause of choroiditis (p 62) The *herpes zoster* virus affects the mesodermal structures of the eye including the uveal tract but ocular damage largely results from the corneal anaesthesia secondary to involvement of the Gasserian ganglion

TREATMENT OF EYE INFECTIONS

Few of the conditions described respond to specific chemotherapy which is only helpful in the relatively uncommon acute bacterial infections and in minimising secondary bacterial contamination associated with the virus infections The broad spectrum antibiotics should be used to treat trachoma and inclusion conjunctivitis partly because they will be beneficial against secondary bacterial invasion and also partly because of their direct effect against these particular viruses

Ophthalmic ointment and/or solutions are available for local administration of the sulphonamides benzylpenicillin tetracycline chloramphenicol polymyxin bacitracin erythromycin neomycin and nystatin This route of administration is of only limited value for the most superficial infections and for deeper penetration subconjunctival administration is necessary The choice of an agent for subconjunctival injection is limited by its solubility The least soluble antibiotics produce irritative reactions if they are given subconjunctivally in any substantial concentration The antibiotics of proven value by this route are 20 000 units of pure benzylpenicillin a 15 per cent suspension of chloramphenicol with adrenaline or a 2 5 to 5 per cent solution of polymyxin with mydricaine They should be given in doses of 0 5 ml daily

Diffusion of the antibiotic into the eyeball following oral or parenteral administration is usually as unreliable as its diffusion into cerebrospinal or synovial fluid and hence the need for local instillation whenever feasible However it should also be given orally to reinforce the local action The most readily diffusible broad spectrum antibiotic is chloramphenicol For tuberculosis oral isoniazid should be given because of its free diffusibility throughout all body fluids

Finally the steroid hormones should be considered for all ophthalmic infections Theoretically they might cause a rapid flare up and spread of infection but in practice this has not proved a problem Whenever possible the cortisone drugs should be used

Parasitic conjunctivitis may be seen in trypanosomiasis, especially with involvement of the eyelids and lacrimal glands in the acute stage of South American trypanosomiasis (Chagas disease) also in loa loa when the nematode migrates across the eye in the vascular epithelium

KERATITIS

The bacterial and viral agents which cause conjunctivitis may involve the cornea causing loss of normal surface vascularisation or even frank ulceration There may also be associated uveitis as in *herpes zoster* infection or *tuberculosis* It is traditional to restrict the term interstitial keratitis to that due to *syphilis*, the congenital form being bilateral, and the much less common acquired form usually affecting only one eye Tuberculous keratitis is becoming increasingly rare and the presence of keratic precipitates on the deep surface of the cornea are more likely to be due to *sarcoidosis* In *leprosy* all degrees of involvement of the cornea may be seen often accompanied by conjunctivitis or uveitis It may be due to direct invasion by Mycobacterium leprae or secondary infection due to neural anaesthetic lesions Corneal ulceration may complicate keratoconjunctivitis in *tularaemia* The corneal ulceration which occurs with *herpes simplex* infection is commonly termed a dendritic ulcer

UVEITIS

The inflammation may predominantly involve the anterior uveal tract as an iridocyclitis or the posterior uveal tract as a choroiditis In most cases the cause of uveitis is unknown and because of this it is popular to fall back on a dubious association with focal sepsis somewhere in the body There is no factual evidence that this is ever responsible for uveitis It is certain that many instances of inflammation of the uveal tract are due to *sarcoidosis* and possibly others may be on the basis of a hypersensitivity mechanism in allergic disorders or even in certain infections

Known and recognisable infections constitute a minority of the causes of uveitis Infection may be due to direct invasion by bacteria or viruses when these are circulating in the blood or by bacteria being introduced through penetrating wounds of the eyeball The resulting uveitis is acute and may even be suppurative Apart from this acute variety the remainder run a more protracted course The known causes are the spirochaetes of *syphilis* and *leptospirosis* the

EAR NOSE SINUSES AND THROAT

EAR

Otitis externa may be associated with furunculosis of the external ear with seborrhoea of the scalp or it may be secondary to chronic infection of the middle ear or mastoid Acute infection may be due to one of the pyogenic organisms particularly *Staph aureus* or *Str pyogenes* whereas a chronic discharge may contain a variety of Gram negative and Gram positive organisms and in addition possibly *Aspergillus fumigatus*

Otitis media is usually due to *Str pyogenes Staph aureus Dipl pneumoniae* or *H influenzae* It may follow sinusitis and pharyngitis and infection may spread along the Eustachian tube Suppuration leads to perforation of the drum of the ear involvement of bone causes mastoiditis or even bacterial meningitis The advent of penicillin has considerably lessened the incidence of pneumococcal meningitis arising from middle ear infection Suppurative middle ear disease complicating the bacterial and virus infections of childhood is now infrequent Nevertheless chemotherapy has not eliminated infection of the middle ear but instead has led to masked infection in which frank suppuration is not obvious The discharge is less conspicuous although it is sufficient to keep the tympanic membrane moist and of a boggy appearance A perforation may in fact heal but painless infection continues to smoulder behind the intact drumhead until its true nature is revealed by the development of an intracranial complication

Treatment

When chemotherapy is indicated the appropriate agent should be given in adequate dosage This may involve systemic or local administration or both routes The bacteriology of the discharge should be obtained for mixed infections may demand a change of antibiotic As soon as the swab has been taken systemic penicillin should be commenced without awaiting the bacteriological report It should be given by intramuscular injection or for children phenoxymethyl penicillin (penicillin V) may be given by mouth The majority of acute infections respond quickly and satisfactorily If not the infecting organism is likely to be a penicillin resistant Staph

together with antibiotics to minimise this threat The early use of the steroids may prevent disabling fibrosis associated with healing This is particularly true in uveitis for they may prevent the development of untreatable chronic fibrotic uveitis Hydrocortisone may be given in the forms of ophthalmic drops and ointment or it may be inoculated by the subconjunctival route in a dose of 6 25 mg in 0 25 ml (25 mg /ml solution) If there is evidence of posterior uveitis it is also important to give prednisolone by mouth because subconjunctival injections are not sufficiently penetrative

cold are due to suppression of secondary bacterial complications This does not warrant their routine use but they should be reserved for patients who are readily prone to complicating sinusitis tracheo bronchitis and pneumonia

Nasal diphtheria demands immediate therapy with specific antitoxin Erythromycin may also be given to suppress the growth of further organisms

SINUSES

When bacterial sinusitis complicates the common cold the invading Gram positive pyogenic cocci are usually those present in the nose and throat When it follows gum infection or tooth extraction the infecting organisms are more likely to be anaerobic bacteria of dental origin Acute sinusitis no longer carries such a sinister risk of orbital cellulitis osteomyelitis cavernous sinus thrombosis septicaemia or brain and lung abscess However it may still be a focus from which infected material may be aspirated into a bronchopulmonary segment or it may be the silent cause of P U O

Treatment

The treatment of choice is intramuscular penicillin which minimises both the bacterial complications of the common cold and the danger of spread of infection during manipulations Local injection is unnecessary for acute sinusitis responds to systemic administration when the causative organism is penicillin sensitive Otherwise oral tetracycline is indicated for it has a wide anti bacterial range and is effective in the treatment of mixed infections

When it is necessary to drain an infected sinus local irrigation may be contemplated The following solutions of antibiotics may be used

Benzylpenicillin	6 000 units per ml
Tetracycline	1 to 5 mg per ml
Polymyxin	1 mg per ml
Bacitracin	500 to 1 000 units per ml

If Ps pyocyanea is present as is often the case with a mixed infection polymyxin should always be used

THROAT

PHARYNGITIS

Pharyngitis like rhinitis has various infective and non infective causes Infection is part of an upper respiratory tract inflammation

aureus or a Gram negative bacillus for which oral tetracycline may be given It is usually unnecessary to give local treatment for an acute infection which responds to systemic chemotherapy Moreover local administration may cause allergic reactions which may confuse the clinical picture of otitis externa If, however, the response to systemic treatment is not as prompt as might be expected it may be supplemented by local instillation of a 10 per cent solution of chloramphenicol in propylene glycol This antibiotic can be used with safety by the local route it causes relatively little local reaction and possesses a wide antibacterial spectrum

The chronic discharging ear poses a more difficult problem for it can be assumed that the above regimes have been ineffective It is invaluable to know the causative organisms and their antibiotic sensitivities before choosing the appropriate antibiotic There may be a *mixed infection which includes Proteus and Ps pyocyanea* The presence of Ps pyocyanea demands polymyxin which may be given as 0 1 per cent ear drops the systemic route is indicated only if there is the suggestion of spread of infection despite local polymyxin Other agents which may be used locally are 10 to 30 per cent sodium sulphacetamide 4 per cent sulphafurazole benzyl penicillin (6 000 units/ml) tetracycline (5 mg /ml with benzocaine in propylene glycol) and bacitracin (500 units/ml)

Finally the appropriate antibiotic may be combined with local hydrocortisone which has proved particularly helpful in reducing the congestion and so relieving the pain of otitis externa

NOSE

Acute rhinitis is a non specific reaction to various infective or non infective insults allergic chemical or atmospheric Infective causes are viruses or bacteria or the combined action of both By far the commonest cause is the unidentified causal agent of the common cold which presents as an acute coryza This is frequently complicated by secondary bacterial invasion which results in a thick purulent nasal discharge

Acute rhinitis may be a prodromal feature of some virus infections including influenza measles smallpox and chicken pox

Corynebacterium diphtheriae may produce diphtheritic lesions

Treatment

There is no specific chemotherapy for these virus infections Claims made for successful antibiotic treatment of the common

necessary for scarlet fever is usually clinically unmistakable and causative organism is readily isolated from the throat

Treatment

Acute streptococcal tonsillitis responds satisfactorily to in muscular penicillin Penicillin lozenges should be avoided altogetl for they have only a superficial effect and cannot be expected penetrate the inflamed tonsils to any worthwhile extent

Prophylactic penicillin or sulphonamides or alternating course each are desirable in the winter months to prevent recurrences individuals who have had one attack of rheumatic fever Prop lactic chemotherapy may also help to abort an impending epide of streptococcal sore throat in a closed community

Chemotherapy does not of course neutralise erythrogenic tc in scarlet fever but penicillin should be given to eradicate the ca organisms from the throat

Peritonsillar abscess (quinsy)

Quinsy is a collection of pus immediately outside the tons mass It is a direct but rare complication of tonsillitis when spr of infection has not been halted by chemotherapy The *treat* is surgical drainage followed by tonsillectomy

FAUCIAL DIPHTHERIA

Following an incubation period of two to seven days fau diphtheria may pre ent as an oedematous nasopharyngitis wi characteristic tonsillar membrane It may or may not be acc panied by toxaemia Nasopharyngeal swabs should be cultured Loeffler s slopes and also on blood agar plates to exclude presence of haemolytic streptococci The Schick skin test (Table indicates whether exposed subjects possess antitoxin capable resisting the disease or whether they are susceptible to infection

Treatment

Early neutralisation of unbound circulating toxin is achievec adequate diphtheria antitoxin as soon as the *clinical* diagnosis been made Depending on the severity between 20 000 and 100 units should be administered intravenously or intramuscularly a intradermal and conjunctival tests have excluded hypersensitivit the foreign serum Test doses consist of 0·2 ml of 1 10 antit

which may include the nose, sinuses and tonsils spread down the respiratory tract is a common sequel Some of the infecting organisms are normal commensals of the pharynx whereas others are only present when it is inflamed Under some circumstances it appears that even commensals may assume pathogenic qualities It is possible that a virus infection may be one agency by which bacteria may become more invasive and cause pharyngitis

Pharyngeal infections may be due to viruses bacteria or both Virus infections include the *adenoviruses influenza* and the *common cold* agent When vesicles are seen in the oropharynx they are commonly due to either *herpes simplex* or *Coxsackie virus* infection

The *pyogenic cocci* are the most frequent pathogens Occasionally Gram negative organisms such as *K pneumoniae* are also found The role of *H influenzae* is not clear it is a normal commensal which may assume pathogenic properties especially in the presence of a virus infection

A better knowledge of the causes of pharyngeal infection will follow improved techniques for virus isolation and identification

Treatment

Chemotherapy is useful only against the bacterial component for the infecting viruses are unaffected by current antibiotics

ACUTE TONSILLITIS

Acute tonsillitis is most commonly due to *Str pyogenes*, and is liable to spread to adjacent areas of the upper respiratory tract The sequelae may be serious since acute streptococcal tonsillitis may provoke rheumatic fever and acute nephritis A chronic carrier of infection may transmit streptococcal infections to contacts or start an epidemic in a susceptible closed community

Scarlet fever

When the β haemolytic streptococci causing tonsillitis produce erythrogenic toxin the diffuse erythematous rash of scarlet fever accompanies the sore throat Specific antitoxin neutralises it and this can be demonstrated by the blanching which follows its intradermal injection (Schultz Charlton reaction Table 24) Conversely the presence or absence of circulating antitoxin may be shown by the intradermal inoculation of erythrogenic toxin which causes erythema and induration in the absence of protective antitoxin (Dick test Table 24) In the individual case these tests are un

Treatment

Oral hygiene and an adequate supply of vitamins prevents the development of conditions in which the fusospirochaetal organisms thrive The established lesions are controlled satisfactorily by penicillin unless aplastic anaemic or leukaemia forms the underlying basis of the disease

LARYNGO TRACHEOBRONCHITIS

This fulminant infection may present the alarming features of laryngospasm and progressive respiratory obstruction (croup) In recent years it has been responsible for childhood epidemics with a high mortality rate It has been causally linked with penicillin resistant *Staph aureus Candida albicans* or thrush infection and to *type b H influenzae* The presence of the latter the epidemic explosiveness of the infection and also the frequent absence of pathogenic bacteria have raised the suspicion that it is due to a virus but none has yet been isolated Smog has also been considered as a contributory factor

This is not a new disease for the clinical picture has for long been recognised as a complication of measles whooping cough and diphtheria However since these have in recent years become milder *infections other causes have become more prominent* The increase of acute laryngo tracheobronchitis due to monilial infection and to penicillin resistant Staph aureus is a heritage of the antibiotic era

In the *diagnosis* retropharyngeal abscess quinsy foreign body in the larynx or an oedematous larynx from non infective or allergic causes must be excluded Bacteriology is helpful in the recognition of diphtheria or other bacterial infections Tissue culture techniques may in the future be helpful in attempts to identify any causal virus

Treatment

Since the cause is often abscure there is no single drug of choice Until results of bacteriology are available tetracycline should be used because it is effective against both Gram positive and Gram negative organisms The child is probably dehydrated and needs infusion of fluids If there is difficulty in swallowing tetracycline may be commenced in this intravenous infusion or alternatively by deep intramuscular injection with procaine until it is tolerated by mouth

intradermally or one drop of 1 100 antitoxin into the conjunctiva If the patient appears sensitive to these small amounts, desensitisation should commence with 0 1 ml of 1 100 antitoxin subcutaneously and thereafter doubling doses every fifteen minutes to a total of 1 ml Any anaphylactic reactions are covered by subcutaneous adrenaline Proceeding cautiously in this way, it should be possible to commence intravenous injections with a similar small dose which is then gradually increased

Complete bed rest minimises circulatory complications, and segregation is continued until two successive daily cultures from nose and throat fail to show virulent organisms

Penicillin erythromycin tetracycline and bacitracin inhibit the in vitro growth of C diphtheriae but do not neutralise the exotoxin Chemotherapy should never be considered as an alternative to antitoxin but only in order to suppress the organisms producing toxin and other secondary invaders and to prevent a chronic carrier state Erythromycin is the drug of choice for this purpose

Exposed and vulnerable contacts should be protected by 1 000 units of antitoxin intramuscularly and at the same time active immunisation with 0 5 ml alum precipitated toxoid (A P T) given in the other arm Four weeks later, a similar dose of A P T should be given The ideal time for routine active immunisation is about the sixth month of life when passive transplacental protection has waned It may be given alone (two doses of 0 5 ml intramuscularly separated by a month) or it may be combined with pertussis vaccine and tetanus toxoid Booster doses during childhood are advisable

VINCENT'S ANGINA

When the protective epithelium of the oropharynx is destroyed or weakened by infection malnutrition and vitamin deficiency, cachexia or by agranulocytosis the normal saprophytic spirochaetes of the mouth combine with anaerobic fusiform bacilli and other oral cocci to cause this ulceromembranous tonsillitis (p 68) The lesion is produced by symbiotic interaction of spirochaetes and fusiform bacilli when necrotic tissue provides a suitable anaerobic environment for their multiplication A similar state of affairs may prevail in chronic lung abscesses bronchiectasis or chronic leg ulcers Throat smears from Vincent s angina always show both fusiform bacilli and spirochaetes The term fusospirochaetal symbiotic disease is therefore more descriptive than Vincent s angina

Treatment

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Treatment

Since the cause is often abscure there is no single drug of choice Until results of bacteriology are available tetracycline should be used because it is effective against both Gram positive and Gram negative organisms The child is probably dehydrated and needs infusion of fluids If there is difficulty in swallowing tetracycline may be commenced in this intravenous infusion, or alternatively by deep intramuscular injection with procaine until it is tolerated by mouth

Antibiotics are only complementary to other measures which include humidification oxygen detergent aerosols or an elective tracheotomy The clinical suspicion of diphtheria is sufficient to demand diphtheria antitoxin

The role of the cortisone drugs in reducing laryngeal oedema has not yet been defined but it should be considered as a life saving measure

CHAPTER 20

VENEREAL DISEASES

SUCCESSFUL chemotherapy has deposed the venereal diseases from their status as one of the biggest medical problems of the late war to relatively insignificant clinical proportions in the well-developed countries However in backward territories they will remain unabated until penicillin prevails over the magic ritual of the witch doctor

SYPHILIS

Natural infection with Trep pallidum is limited to man who is infected either by sexual intercourse or by transplacental spread With better treatment and earlier diagnosis all types of syphilis are now becoming rare The disease passes through three stages—primary secondary and tertiary

Primary stage Two to ten weeks after exposure a small hard ulcer (chancre) appears on the genitalia or less often on the mouth or breast Related lymph nodes are enlarged The chancre heals within ten weeks leaving a scar

Secondary stage In the course of six months a generalised maculopapular rash and lymphadenopathy may develop Moist pale papules (condylomata) appear at mucocutaneous junctions especially the ano-genital region and mouth Meningitis arthritis or osteitis may occur but they tend to heal spontaneously within a few weeks

Tertiary stage One-quarter of patients with primary or secondary syphilis have a spontaneous complete cure and a similar number have no further overt signs of syphilis although serological tests remain positive The remainder after a latent period which may extend over many years develop manifestations of tertiary syphilis These include a granulomatous lesion (gumma) which is found in skin bones liver and central nervous system cardiovascular lesions especially aortitis and central nervous system disease shown by meningovascular lues general paralysis of the insane or tabes dorsalis

Congenital syphilis The pregnant syphilitic woman can infect her offspring with spirochaetes transplacentally This may result in early miscarriage in later still births or in the birth of a live syphilitic child Neonatal syphilis is characterised by rashes

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The role of the cortisone drugs in reducing laryngeal oedema has not yet been defined but it should be considered as a life saving measure

Flocculation tests (Kahn Hinton Mazzini Price etc) The lipid antigen remains dispersed in normal serum but flocculates in syphilitic serum

These serological tests become positive within two or three weeks of infection and remain positive throughout the secondary stage of infection In the tertiary phase positive results can be expected in only 75 per cent of cases When cerebrospinal fluid is used up to 10 per cent of fluids from patients with clinical tabes but fewer from patients with general paralysis of the insane give negative results The spinal fluid is always positive in meningovascular syphilis

False positive serological tests The reactive antibodies of syphilitic serum which are concerned with positive complement fixation and flocculation tests are located in globulins usually the euglobin fraction It is not surprising therefore that other diseases in which this fraction is increased may give a falsely positive result It is nearly always positive in yaws and transient positive reactions may occur in nfectious mononucleosis lymphogranuloma venereum lymphocytic horiomeningitis virus pneumonia malaria trypanosomiasis After mallpox vaccination there may be a transient positive reaction It is l erefore important to repeat the test at intervals by different methods efore commencing antisyphilitic treatment In collagen diseases ..ch as periarteritis nodosa or lupus erythematosus and in hepatic irrhosis a false positive result may persist but the clinical picture is ually quite distinctive

Positive serology in an otherwise healthy individual who denies fection can be very difficult to evaluate If both tests are repeatedly ositive specific neutralising antibodies can be sought in the atient s serum by the treponema pallidum immobilisation test This depends on immobilisation of live motile spirochaetes since se are not readily available this time-consuming test is not yet acticable in a routine laboratory If there is any doubt treatment ould be instituted

revention

The steady decline in syphilis has followed not only specific motherapy but also education of the public and earlier diagnosis venereal diseases Congenital syphilis is rarely seen since routine assermann reactions have been performed during pregnancy

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jaundice and mucocutaneous condylomata In later life congenital syphilis manifests itself by saddle nose Hutchinson s teeth deafness interstitial keratitis perforated palate and tabo paresis

DIAGNOSIS (Table 23)

Demonstration of the spirochaete

Since organisms disappear within a few hours of commencing treatment they should be sought before treatment is begun Tissue fluid expressed from surface lesions is examined by dark ground illumination for the typical motile spirochaetes Repeated examination of fluid from the chancre mucocutaneous condylomata and skin eruptions is nearly always positive The liver of the congenital syphilitic is teeming with spirochaetes

Spirochaetes are not usually found in tertiary stage lesions

TABLE 23 —VENEREAL DISEASES

Infection	Causal agent	Diagnostic tests	Drug of choice
Syphilis	Treponema pallidum	1 Demonstration of organism from chancre 2 Blood and C S F Wassermann or Kahn 3 Treponema immobilisation	Penicillin
Gonorrhoea	Neisseria gonorrhoeae	Direct examination and culture of organism from urethral discharge	Penicillin
Lymphogranuloma venereum	L G V virus	1 Cultivation of virus in yolk sac of chick embryo 2 Complement fixation 3 Frei skin test	Tetracycline
Granuloma inguinale	Donovania granulomatis	Direct examination and cultivation on egg containing media	Tetracycline
Soft sore (chancroid)	Haemophilus ducreyi	Isolation of organism from sore	Sulphadiazine
Non-specific urethritis	?	—	?Tetracycline

Serological tests

The complement fixation test (Wassermann reaction) depends on the ability of syphilitic serum to fix complement in the presence of an antigen consisting of an alcoholic extract of the lipids of beef heart

Flocculation tests (Kahn Hinton Mazzini Price etc) The lipid antigen remains dispersed in normal serum but flocculates in syphilitic serum

These serological tests become positive within two or three weeks of infection and remain positive throughout the secondary stage of infection In the tertiary phase positive results can be expected in only 75 per cent of cases When cerebrospinal fluid is used up to 10 per cent of fluids from patients with clinical tabes but fewer from patients with general paralysis of the insane give negative results The spinal fluid is always positive in meningovascular syphilis

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Positive serology in an otherwise healthy individual who denies infection can be very difficult to evaluate If both tests are repeatedly positive specific neutralising antibodies can be sought in the patient s serum by the treponema pallidum immobilisation test This depends on immobilisation of live motile spirochaetes since these are not readily available this time-consuming test is not yet practicable in a routine laboratory If there is any doubt treatment should be instituted

Prevention

The steady decline in syphilis has followed not only specific chemotherapy but also education of the public and earlier diagnosis of venereal diseases Congenital syphilis is rarely seen since routine Wassermann reactions have been performed during pregnancy

One injection of 2 million units of a long acting penicillin preparation will prevent the development of syphilis in individuals who have been exposed to it in the preceding two weeks

Treatment

Penicillin has superseded other treatments for all varieties of the disease An adult dose of approximately 1 million units of a long acting penicillin is given intramuscularly once daily for ten to fourteen days This course is used in the primary and secondary stages for gummata for cardiovascular and for latent syphilis A gumma may take up to two months to heal following this treatment In addition to penicillin selected aortic aneurysms may be resected and replaced by homografts Cardiac failure is treated along the usual lines

Neurosyphilis should be given the benefit of a slightly longer course of treatment lasting three weeks but there is no advantage in intrathecal administration of penicillin In tabes dorsalis and general paralysis of the insane irreparable destruction has occurred This does not preclude penicillin which may halt further deterioration If improvement is not striking or not maintained it is worth considering the addition of fever therapy induced by malaria

The *pregnant* syphilitic mother should be given a standard ten day course of treatment and it is wise to repeat it in subsequent pregnancies

The infant with *congenital syphilis* is treated on the basis of a total course of 500 000 units/kg in divided doses over ten days or 150 000 units of procaine penicillin daily for ten days To prevent subsequent scarring due to interstitial keratitis an initial subconjunctival injection of 6 25 mg of hydrocortisone should be followed by 1 per cent hydrocortisone eye drops for this condition The outlook is better if congenital syphilis is diagnosed and treated within the first three months of life

If for some very clear reason penicillin cannot be used for treatment tetracycline should be given in doses of 2 g daily for two to three weeks

Jarisch Herxheimer reaction Fever with exacerbation of the syphilitic lesion may follow treatment The reaction is presumably allergic due to destruction of organisms in areas previously sensitised to the syphilitic antigen This reaction is of importance where the syphilitic lesion is in a vital structure such as brain or aorta and the mouth of the coronary arteries This complication has led to the use of gradually increasing doses of penicillin in the treatment of tertiary syphilis but since the reaction is not dependent on the amount of drug used this does not prevent its development

Potassium iodide and bismuth are often given before penicillin There is no factual evidence to suggest that they minimise the frequency of Herxheimer reactions

Follow-up

Treatment should be followed by serological tests and cerebro spinal fluid examinations at intervals up to five years from com mencing treatment Spinal fluid examination of patients with neurosyphilis should by repeated at least twice in the first year and thereafter annually The leucocyte count is the best index of persisting activity because the Lange curve and Wassermann reaction may take many years to revert to normal after treatment If the cell count is normal six months after treatment it is safe to predict that it will remain so permanently If it is raised a further course of penicillin therapy should be given

GONORRHOEA

Gonorrhoea is still prevalent although a world wide decline has inevitably followed the introduction of specific chemotherapy It is almost always acquired by sexual intercourse and it is clinically evident within one week of this act Ophthalmia neonatorum is acquired during passage through the birth canal of the infected mother

The organism attacks the mucous membrane of the genital tract and eye In the male a painful purulent urethritis may be followed by spread to prostate seminal vesicles and epididymis In the days before chemotherapy healing was often accompanied by fibrosis and stricture formation in the urethra In the female the initial urethritis is followed by spread to vagina cervix uterus and Fallopian tubes Chronic gonococcal salpingitis used to be an important cause of sterility

With modern method of treatment spread from the initial urethral lesion is rare as indeed are such sequelae as metastatic arthritis and iridocyclitis or ophthalmia neonatorum and epidemic vulvovaginitis in children

The diagnosis (p 87) is confirmed by isolation of the causal organism from the discharge (Table 23)

Prevention

Prevention of the disease is assured by a single intramuscular injection of 300 000 units of procaine penicillin soon after exposure

Treatment

Penicillin has superseded other treatments for all varieties of the disease An adult dose of approximately 1 million units of a long acting penicillin is given intramuscularly once daily for ten to fourteen days This course is used in the primary and secondary stages for gummata, for cardiovascular and for latent syphilis A gumma may take up to two months to heal following this treatment In addition to penicillin selected aortic aneurysms may be resected and replaced by homografts Cardiac failure is treated along the usual lines

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as a control Specific induration at two days indicates that the patient is or has been at some time in his life infected with the viruses of the psittacosis lymphogranuloma group It is no more specific than this and should be evaluated in the light of the clinical picture and serological results

Treatment

The sulphonamides tetracyclines and chloramphenicol have all proved effective Tetracycline in doses of 2 g by mouth daily for ten days may be sufficient to treat an early infection but it should be prolonged for one month or repeated courses given if resolution appears to be slow

GRANULOMA INGUINALE

Hitherto this has been a rare venereal disease in Great Britain although it is endemic in various subtropical areas including the West Indies With the substantial increase of immigrants from this area in recent years more instances may be seen As well as being commoner in the coloured races it is also more frequent in women An indurated erythematous papule or vesicle of the genitalia or perineum breaks down to form a painless ulcer with rolled edges and a granulomatous floor Secondary infection may convert this into a painful foul smelling and sloughing area with a subsequent attempt at healing by scar tissue formation

Diagnosis i established by finding the causative organism *Donovania granulomatis* in Giemsa or Leishman stained films of scrapings from the lesion The Donovan bodies are found lying free or in the cytoplasm of large monocytes They may be cultivated on egg yolk media

Treatment

The organism is sensitive to streptomycin the tetracyclines and chloramphenicol The drug of choice is tetracycline which should be given in doses of 2 g daily for a week and then continued in doses of 1 g daily for a further three weeks to prevent a relapse of infection

CHANCROID OR SOFT SORE

H ducreyi is a minute Gram negative bacillus about 1 μ in length which causes a chancroid or soft ore on the genitalia within two weeks of sexual intercourse It commences as a pustule with

Penicillin eye drops soon after birth prevent the development of ophthalmia neonatorum

Treatment

Although gonococci have shown resistance to sulphonamides they remain sensitive to penicillin For acute anterior urethritis a single intramuscular injection of 600 000 units of procaine penicillin suffices but if there is involvement of the prostate epididymis or seminal vesicles this dose should be continued daily for one week This longer course is also advisable when the Fallopian tubes are involved

Cultures should be repeated at weekly intervals for one month and if further organisms are isolated a week s course of intramuscular penicillin should be administered Because concomitantly acquired syphilis may be masked by this treatment blood Wassermann reactions should be performed at three and six months after the completion of treatment

LYMPHOGRANULOMA VENEREUM

This venereal disease is caused by a virus closely similar to the psittacosis virus Following an incubation period of up to three weeks after sexual intercourse the genitalia become the site of a vesicle which progresses to a shallow, greyish ulcer It is most commonly found on the glans prepuce or in the coronary sulcus, and in the female on the labia or posterior vaginal wall A week or two after this primary lymphogranulomatous chancre there is enlargement of the regional lymph nodes to form buboes which become the seat of draining abscesses The untreated case may progress to stricture formation or elephantiasis of the genital tract anus or rectum

Lymphogranuloma shows a conspicuous predilection for the male sex This may be a deceptive observation because the development of inguinal lymphadenitis in the male is more obvious than regional involvement of the pelvic lymph nodes in the female

Diagnosis (p 131 Tables 11 and 23) is confirmed by isolation of the causative virus by demonstration of a significant rise in complement fixing antibodies or by means of the Frei test (Table 24)

Frei prepared his original antigen from bubo pus obtained from patients with lymphogranuloma venereum *Lygranum* antigen is now prepared from virus cultivated in the yolk sac of the fertile egg Skin tests should include uninfected yolk sac suspension

as a control Specific induration at two days indicates that the patient is or has been at some time in his life infected with the viruses of the psittacosis lymphogranuloma group It is no more specific than this and should be evaluated in the light of the clinical picture and serological results

Treatment

The sulphonamides tetracyclines and chloramphenicol have all proved effective Tetracycline in doses of 2 g by mouth daily for ten days may be sufficient to treat an early infection but it should be prolonged for one month or repeated courses given if resolution appears to be slow

GRANULOMA INGUINALE

Hitherto this has been a rare venereal disease in Great Britain although it is endemic in various subtropical areas including the West Indies With the substantial increase of immigrants from this area in recent years more instances may be seen As well as being commoner in the coloured races it is also more frequent in women An indurated erythematous papule or vesicle of the genitalia or perineum breaks down to form a painless ulcer with rolled edges and a granulomatous floor Secondary infection may convert this into a painful foul smelling and sloughing area with a subsequent attempt at healing by scar tissue formation

Diagnosis is established by finding the causative organism *Donovania granulomatis* in Giemsa or Leishman tained films of scrapings from the lesion The Donovan bodies are found lying free or in the cytoplasm of large monocytes They may be cultivated on egg yolk media

Treatment

The organism is sensitive to streptomycin the tetracyclines and chloramphenicol The drug of choice is tetracycline which should be given in doses of 2 g daily for a week and then continued in doses of 1 g daily for a further three weeks to prevent a relapse of infection

CHANCROID OR SOFT SORE

H ducreyi is a minute Gram negative bacillus about 1 μ in length which causes a chancroid or soft sore on the genitalia within two weeks of sexual intercourse It commences as a pustule with

surrounding oedema and erythema the centre breaks down into a necrotic ulcer with irregular undermined edges and the draining lymph nodes may suppurate Soft sore does not have the induration characteristic of a syphilitic chancre

Diagnosis is confirmed by preparation of stained smears from the ulcer or by culture of the organism in special media

Treatment

The sulphonamides tetracyclines chloramphenicol and streptomycin are all effective but there is no response to penicillin Because of the risk of masking a concomitant syphilitic infection with a broad spectrum antibiotic the drug of choice is a sulphonamide If there is no response to this treatment it is not then too late to perform darkground examinations of scrapings from the lesion for Trep pallidum The blood Wassermann reaction should also be done as a precaution up to six months after treatment of chancroid

NON SPECIFIC URETHRITIS

The occurrence of urethritis for which no causal organism is found is a difficult diagnostic and therapeutic problem On occasions both pleuropneumonia like and trichomonas like organisms have been isolated from the discharge but it is possible that an as yet, un identified virus may be the causal agent Recurrence or perpetuation of the infection may be due to an untreated focus of infection in the consort When all possible known causes have been excluded empirical treatment with 1 g tetracycline daily for a week is justifiable A recurrence is an indication for prescribing a similar course of treatment to the consort

CONTINUED PYREXIA OF UNKNOWN ORIGIN (P U O)

THIS term is usually applied to a continuing pyrexia in the absence of localising symptoms and signs A systematic approach to its elucidation includes a careful history daily physical examination four hourly records of temperature and pulse and selected investigations When involvement of a specific system is disclosed efforts are directed to its investigation and the patient is no longer regarded as an ambiguous P U O

The concept of P U O has changed with the advent of chemotherapy Inadequate treatment may mask certain phenomena although fever persists Blunderbuss treatment should be avoided for this may abort an illness before localisation occurs and diagnosis in retrospect is impossible

CLINICAL

The history is obviously important the patient is questioned about the mode of onset and duration periodicity and recurrences of the febrile episodes and whether accompanied by rigors Contact with infections overseas residence and previous fevers are noted Localising symptoms such as sore throat or cough are elicited An associated constitutional upset with headache rigors and generalised aches is suggestive of a stage of bacteriaemia or viraemia The patient is *examined* frequently for the development of any localising signs (Fig 1)

The *temperature chart* may suggest malaria Hodgkin s disease typhoid or relapsing fever

INVESTIGATIONS

A mid stream or catheter specimen of *urine* is centrifuged and the unstained deposit examined microscopically for leucocytes erythrocytes and motile organisms The deposit is then stained by Gram s method The specimen is also cultured Fouchet s test for bilirubin may be positive in the early anicteric stage of virus hepatitis or of drug jaundice (e g chlorpromazine jaundice)

The *faeces* should be scrutinised for mucus blood or parasites and

the colour and consistence noted A warm specimen is examined microscopically for amoebae and cultured

Throat swabs are examined for Str pyogenes even if there is no obvious local lesion Cultures are set up for other organisms, including C diphtheriae if clinical suspicion warrants it

A *leucocyte count* and stained blood film are essential A poly

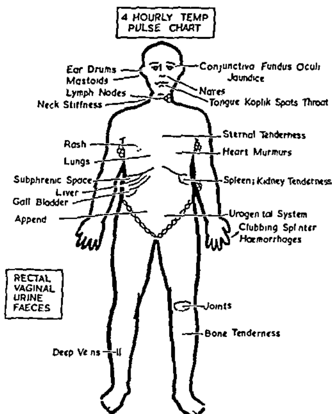


FIG 1—Examination of patient with fever

morphonuclear leucocytosis suggests bacterial infection whereas a relative lymphocytosis with a normal total leucocyte count points to a virus infection or possibly tuberculosis The presence of abnormal mononuclear cells non specifically suggests a virus infection but numerous glandular fever cells' are virtually diagnostic of infectious mononucleosis Other abnormalities of leucocytes may indicate leukaemia or multiple myelomatosis Special tech

niques may disclose disseminated lupus erythematosus If there is clinical suspicion blood smears should be searched for malaria parasites or various spirochaetal organisms such as leptospirae

Chest radiography is performed even if the history and examination do not suggest pulmonary disease

Blood culture is routinely performed preferably at the height of the fever and it is repeated at frequent intervals The blood should be incubated under aerobic and anaerobic conditions

Serum for *antibody levels* is obtained early in the illne s as a baseline for comparison with convalescent phase sera High and especially rising titres may indicate recent infection with brucella salmonella leptospira toxoplasma or rickettsial organisms or with the viruses of the lymphogranuloma psittacosis group influenza lymphocytic choriomeningitis or herpes simplex In addition to these tests for specific antibodies there are certain non specific tests which are helpful These include the Paul Bunnell test for the diagnosis of infectious mononucleosis the Weil Felix reaction for rickettsial infections and tests for streptococcus M G agglutinins and cold haemagglutinins in virus pneumonia

A *lumbar puncture* is performed if there is persistent headache or the suspicion of meningism The pressure of the cerebrospinal fluid is recorded the appearance noted a cell count performed and smears stained by Gram s method and for acid fast bacilli The fluid is cultured for fungi as well as bacteria The protein and glucose levels in the fluid should also be determined (Table 18)

If a diagnosis cannot be established by the above routine other possibilities must be considered

1 A localised collection of *pus* in the pleura kidneys liver sub phrenic spaces bone or brain Alternatively intra abdominal or pelvic abscess may have followed an unsuspected gastro intestinal perforation Further investigations are directed towards localisation and aspiration of the pus
2 *Collagen diseases* may be extremely difficult to diagnose during the early febrile stage Rheumatoid arthritis disseminated lupus erythematosus polyarteritis nodosa and dermatomyositis should be considered Investigations are directed towards histological demonstration of the lesion and biopsy of skin muscle liver or kidney may be considered The L E cell phenomenon may be seen in peripheral blood or bone marrow

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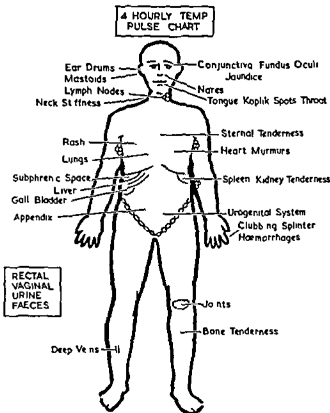


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CHAPTER 22

THE USE OF CORTICOSTEROIDS IN THE MANAGEMENT OF INFECTIONS

CONSIDERABLE controversy surrounds the use of the cortisone group of drugs in the presence of infections It is well recognised that they may exert profound and harmful effects With their widespread use and an increasing number of routes of administration available there can be but few practitioners who have not observed exacerbations or spread of infection as a complication of cortisone therapy The mechanism of the adverse effects remains conjectural although it must in some way either affect the multiplication of micro-organisms depress host defence mechanisms or influence the inflammatory response provoked by the invading organism

A simple stimulant effect on the growth of the infective agent would be a surprising explanation for it would imply a similar metabolic response by such diverse micro-organisms as fungi protozoa bacteria rickettsiae and viruses all of which have been shown to be affected by corticosteroids Indeed for a single drug to have such a sweeping range of activity would be the envy of the broadest of antibiotics

A suppressive effect on defence mechanisms might involve inhibition of antibodies or phagocytes either directly or through an intermediate effect on the reticulo-endothelial system Cortisone has been shown to interfere with a rapid rise in circulating antibody titre although it does not alter the rate of disappearance of passively administered antibody This suggests that the hormone interferes with antibody synthesis This sequence of events however could hardly account for clinical changes which may take place as soon as a day after commencing steroid therapy Neither would it account for increased virus multiplication in cortisone treated chick embryos devoid of antibody The effect of adrenocortical hormones on phagocytic cells has been the subject of investigation and because of conflicting results also a subject for speculation This lack of knowledge is enhanced by our ignorance of the role of the various cells concerned with inflammation There is little doubt but that cortisone fundamentally alters the vascular and cellular response to infection Capillary and arteriolar tone is increased endothelial swelling reduced permeability to plasma proteins diminished and

3 *Reticulosis* especially Hodgkin s disease may masquerade as an undiagnosed pyrexia which is either continuous or interrupted by afebrile periods The latter is liable to be misinterpreted as a successful response to antibiotic therapy until recurrence arouses suspicion of a Pel Ebstein type of fever

4 Intermittent pyrexia may complicate *hepatic cirrhosis* and this complication should always be considered The physical signs of the liver disease supported by biochemical abnormalities, are usually diagnostic

5 *Neoplasms* may present as a 'P U O ' presumably because of necrosis within the tumour mass In certain sites of development they may remain silent and a continued pyrexia constitutes the only early evidence of the disorder Hypernephroma and hepatoma are liable to present in this way but hepatic metastases from any source including those from a malignant melanoma should be considered Retroperitoneal tumours including sarcoma may commence with no signs other than pyrexia because their situation makes early clinical recognition difficult

Despite a systematic approach and exhaustive investigation there remains a large group of pyrexias which defy present day methods of diagnosis At this stage and only when all possible causes have been adequately investigated it is permissible to embark on a therapeutic trial of various drugs which may provide significant information The response to emetine injections for instance may provide suggestive evidence of hepatic amoebiasis When the sulphonamides and antibiotics are employed in this context it is wise to commence with the drug which has the narrowest bacterial spectrum If this agent is without effect it may be necessary to resort in turn to antibiotics with a wider range of action It may be possible to infer from this empirical trial whether or not the pyrexia is due to an antibiotic sensitive organism and if so whether this may be Gram positive or Gram negative rickettsia or a large virus (of the psittacosis group) A suggested schedule should commence with penicillin and be followed if necessary by streptomycin and then tetracycline

Anti Inflammatory

When inflammatory exudate causes congestion in an unyielding space pain and tenderness may cause marked distress By reducing inflammation the cortisone drugs provide marked relief of symptoms Within twenty four hours of commencing treatment there is dramatic relief of pain tenderness and swelling of *mumps orchitis* with corresponding subsidence of pyrexia Similar relief of congestion with lessening of pain occurs in *otitis externa* Intraneural inflammatory exudate may cause persistent and painful neuritis in *leprosy* for which intraneural injections of hydrocortisone with procaine produce symptomatic relief Steroid therapy may have a place in reducing laryngeal oedema, which accompanies acute *laryngo-tracheobronchitis*

These examples outline the possible benefits of an early reduction of acute inflammatory oedema The hormones are also known to influence the later stages of inflammation by preventing the normal development of granulation and subsequent dense fibrosis In view of all these powerful anti inflammatory effects local hydrocortisone has been recommended for *syphilitic interstitial keratitis* as well as *uveitis*

Encouraging results are being observed by the combined use of cortisone and anti tuberculous chemotherapy in certain forms of pulmonary and meningeal *tuberculosis* The value of steroid therapy in tuberculosis is currently being investigated in several therapeutic trials but indiscriminate use even under cover of anti tuberculous drugs should be discouraged Much more information must accrue before it can be said that the value of the corticosteroids outweighs their disadvantages

Anti Allergic

Cortisone therapy may be invaluable in averting alarming allergic reactions associated with certain infections or of the vaccines or antibiotics used in their treatment On this basis the cortisone drugs may be indicated in *trichiniasis* ruptured *hydatid cyst* or to control asthma due to pulmonary migration of certain *helminths* They are effective in controlling iridocyclitis erythema nodosum and acute sulphone sensitisation in *leprosy*

Acute disseminated encephalomyelitis following certain virus infections such as measles chicken pox and rubella or following vaccination against smallpox or rabies may be favourably influenced

the cellular components of the inflammatory exudate change Whereas these modifications may prove favourable in collagen diseases or hypersensitivity reactions they may contribute adversely *to inflammation due to infection by encouraging spread of* micro organisms causing further necrosis or caseation and by preventing the normal development of granulation tissue and of healing

These dangers should be sufficient to veto the use of cortisone in all infections Nevertheless paradoxical though it may seem the Addisonian patient who used to be highly susceptible to infection is now well controlled and free from infection despite continuous treatment with these same drugs Furthermore, favourable reports have followed the deliberate use of corticosteroid therapy in over whelming infections which would otherwise have proved fatal It is now clear that these potentially dangerous drugs may prove beneficial in a few infections as long as they are used in conjunction with specific chemotherapy

The indications for the use of hormone therapy is at present in an ill defined exploratory stage They may be classified according to the probable mechanisms by which a favourable response is obtained namely anti toxic anti inflammatory and anti allergic However it must be realised that this classification remains arbitrary until the precise influence of the steroids on infectious processes is better understood It is probable that more than one factor is operative in each instance

Anti Toxic

A dramatic suppression of symptoms and lessening of toxaemia within twenty four hours of commencing steroid therapy may halt deterioration in an overwhelming infection sufficiently to allow antibiotics to take effect Their use under these grave circum stances has been described as the principle of buying time it appears justifiable when the alternative is almost certainly death The response seems to be more dramatic in the profoundly toxaemic patient especially when the infection is accompanied by the release of endotoxins These infections are due to *brucellae salmonellae meningococci* and *rickettsiae* and the same striking response has also been observed in fulminant *infective hepatitis* Steroid therapy may also be justifiable in severe *glandular fever* complicated by hepatic involvement or encephalomyelitis

TABLE 24—SKIN TESTS

Test	Antigen	Remarks
Delayed type Hypersensitivity		
Mantoux	Old tuberculin or P P D	
Brucellin	Heat killed brucella organisms	Skin test may increase serum antibody titre in previously sensitised
Coccidioidin	Extract Coccidioides immitis	
Histoplasmin	Extract Histoplasma capsulatum	
Pertussis	Pertussis agglutinogen	
Toxoplasmin	Peritoneal fluid of infected mice	Results parallel neutralising antibody titre Skin test may increase serum antibodies in previously sensitised
Trichinella	Extract dried trichinella larvae	
Trichophytin	Extract trichophyton gypseum	
Tularaemia	Detoxified suspension Past tularense	
Frei (modified)	Yolk sac culture L G V virus	Control with uninfected egg material essential to exclude egg-sensitive individual
Herpes simplex	Infected allantoic fluid	
Mumps	Infected allantoic fluid	
Lepromin	Lepra bacilli or lepromatous tissue	
Fernandez		Induration at 48 hours — Useful for prognosis and classification but of no diagnostic value
Mitsuda		Nodule or ulcer in 28 days — Useful for prognosis and classification but of no diagnostic value
Immediate Type Hypersensitivity		
Casoni	Sterile fluid from hydatid cyst	Immediate wheal with surrounding erythema indicates previous leakage of hydatid cyst
Trichinella	as for delayed type hypersensitivity	Immediate wheal and erythema followed by delayed type hypersensitivity
Toxin-antitoxin Neutralisation		
Dick	Haemolytic streptococcus toxin	Induration and erythema > 10 mm. at 24 hours indicates susceptibility to scarlet fever
Schick	$\frac{1}{50}$ M L D diphtheria toxin	Induration and erythema > 10 mm at 48-96 hours indicates susceptibility to diphtheria
Schultz Charlton	Scarlet fever antitoxin	Blanching > 10 mm in scarlatiniform rash indicates that rash is due to scarlet fever toxin

Skin tests used in the diagnosis of infections may reveal delayed type (tuberculin type) or immediate type (histamine type or anaphylactic) hypersensitivity or they may depend on toxin-antitoxin neutralisation The intradermal dose is 0·1 ml except for the Schick and Casoni tests in which 0·2 ml is inoculated

Delayed type skin reactions are elicited by the injection of the organisms or their products and read 48 hours later A positive reaction consists of induration greater than 5 mm in diameter with possible surrounding erythema The area of induration for positive toxoplasmin, trichophytin and lepromin tests is usually laid down as greater than 10 mm A positive result indicates past or present infection with the organism concerned It does not necessarily imply that the patient is suffering from that particular disease The interpretation of all delayed type skin tests is the same as for the prototype, the Mantoux reaction

Immediate-type reactions consist of a wheal with surrounding erythema within 30 minutes of the intradermal injection

Toxin-antitoxin neutralisation tests are now rarely used

by steroid therapy, for the common pathogenesis is probably anaphylactic sensitisation

Sensitisation to antibiotics particularly penicillin and streptomycin may provoke troublesome complications If it is essential to continue treatment with either of these drugs corticosteroid therapy may provide an invaluable cover

In summary it should be stressed that there are relatively few indications for the use of steroid therapy in the management of infections When indicated they should, whenever possible, be given together with specific chemotherapy Since their influence is usually early and dramatic it is not often necessary to prescribe them for longer than a few days and withdrawal should be gradual to avoid relapses The most effective and least toxic oral preparations in current use are prednisone and prednisolone and either is indicated for systemic use Whenever possible topical use of hydrocortisone should be given instead of or in addition to oral therapy for a maximal effect in the shortest time

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